Grundlagen evidenzbasierter Rehabilitation von Schizophrenieerkrankten

Basics of evidence-based Rehabilitation in individuals with schizophrenia

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Dedicated to

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The patients with schizophrenia and their families, who participated in this research project

and my family

Η ιδιαίτερη υπεροχή του ανθρώπου είναι αυτή που τον διακρίνει από τα ζώα, δηλαδή η λογική

Αριστοτέλης

Logic is the human's special attentiveness that distinguishes him from animals

Aristotle

Η εκπαίδευση είναι η δύναμη που γιατρεύει τη ψυχή

Πλάτωνας

Education is the power that heals the soul

Platon

Science is organized knowledge. Wisdom is organized life

Immanuel Kant

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Abstract

Schizophrenia is a chronic mental health disorder, which changes rapidly the life of the persons and their families, who suffer from it. It causes high biological and psychological vulnerability as well as cognitive, emotional and behavioral disorders. Nowadays, evidence-based pharmacotherapy and psychotherapy are available aiming the rehabilitation and recovery of individuals with schizophrenia. A democratic society is obliged to give these people the opportunity to have an access to those treatments.

The following three published studies present this dissertation thesis and have a common focus on the implementation of evidence-based psychotherapy in individuals with schizophrenia.

The first study evaluates the efficacy of the Integrated Psychological Therapy (IPT) in Greece, one of the most evaluated rehabilitation programs. IPT was compared to Treatment as Usual (TAU) in a randomized controlled trial (RCT) with 48 individuals with schizophrenia. Significant effects favouring IPT were found in working memory, in social perception, in negative symptoms, in general psychopathology and in insight. This study supports evidence for the efficacy of IPT in Greece.

The second study evaluates a second hypothesis, when IPT is more and less effective regarding treatment resistant schizophrenia (TRS) and non treatment resistant schizophrenia (NTRS). It is a part of the first paper. Significant effects favouring NTRS were found for verbal memory, for symptoms, for functioning and quality of life. Effect sizes showed superiority of NTRS in comparison to TRS. IPTTRS showed on the other side some significant improvements. This study presents the initial findings of a larger study to be conducted internationally for the first time.

The third study is a systematic review, which aims to evaluate the efficacy of Cognitive Behavioral Therapy (CBT), of Meta Cognitive Therapy (MCT), Metacognitive Training (MCTR), Metacognitive Reflection and Insight Therapy (MERIT), of various Rehabilitation Programs and Recovery Programs in individuals with schizophrenia. 41 RCTs and 12 Case Studies were included. The above interventions are efficacious in the improvement of cognitions, symptoms, functional outcome, insight, self-esteem, comorbid disorders and metacognitive capacity.

The three studies provide insight regarding the importance of evidence-based psychotherapy in persons with schizophrenia leading to recovery and reintegration into society. Future RCTs with larger samples and long-term follow up, combining evidence-based psychotherapies for individuals with schizophrenia need to be done.

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CACR: Computer assisted cognitive remediation

CBT: Cognitive behavioral therapy

CET: Cognitive Enhancement Therapy

CPT: Continuous Performance Test

CR: Cognitive Remediation Therapy

DSM V: Diagnostic and Statistical Manual of Mental Disorders

EPHPP: Effective Public Health Practice Project

GAF: Global Assessment of Functioning

GLM: General Linear Model

IMR: Illness Management and Recovery Program

IPAP: International Psychopharmacology Algorithm Project

INT: Integrated Neurocognitive Therapy

IPT: Integrated Psychological Therapy

LNS: Letter Number Span

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCT: Metacognitive Therapy

MCTR: Metacognitive Training

MERIT: Metacognitive Reflection and Insight Therapy

MIT-P: Metacognitive Interpersonal Therapy for Psychosis

NICE: National Institute for Care and health Excellence

NIMH: National Institute of Mental Health

NTRS: Non treatment resistant schizophrenia

PANSS: Positive and Negative Syndrome Scale

RCT: Randomized Controlled Trial

SPSS: Statistical Package for the Social Sciences

SPS: Social Perception Scale

TAU: Treatment as Usual

TRS: Treatment Resistant Schizophrenia

VMT: Verbal Memory Test

WAIS: Wechsler-Intelligenztest for Adults

WRAP: Wellness Recovery and Action Planning Program

WHOQOL: Quality of Life Scale

1. Schizophrenia: psychopathology and treatment

1. 1. Introduction

Schizophrenia is a chronic mental health disorder, which determines negatively the life of individuals with schizophrenia and their families. It presents a great burden with negative consequences in emotional, behavioral and intepersonal level.

Following diagnostic criteria must fulfil schizophrenia 295.90 (F20.9), according to DSM V (American Psychiatric Association, 2013):

A. Two (or more) of the following, each present for a significant portion of time during a 1 -month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.

2. Hallucinations.

3. Disorganized speech (e.g., frequent derailment or incoherence).

4. Grossly disorganized or catatonic behavior.

5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms.

During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences) (APA, 2013).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness (APA, 2013).

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (APA, 2013).

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only, if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated) (APA, 2013).

The main features of schizophrenia are positive symptoms (Delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior), negative symptoms (diminished emotional expression, avolition, alogia, anhedonia, social withdrawal), mood disorders (APA, 2013) and cognitive dysfunctions (APA, 2013; Bell, Corbera, Johannessen, Fiszdon, & Wexler 2013; Fett, Maat, & Group Investigators, 2013; Fioravanti, Bianchi, & Cinti, 2012; Green et al., 2008; Green et al., 2012; Hovington, Bodnar, Joober, Malla, & Lepage, 2013; Nuechterlein & Green, 2006; Roder & Mueller, 2008; Sachs, 2008; Savla, Vella, Armstrong, Penn, & Twamley, 2013; Ventura, Tom, Jetton, & Kern, 2013).

The National Institute of Mental Health (NIMH) supported the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. The following cognitive domains are relevant for the treatment of schizophrenia: Neurocognition (speed of processing, attention/vigilance, verbal and visual memory, working memory, reasoning and problem solving) and social cognition (emotion processing, social perception, Theory of Mind (TOM), social schema, attribution) (Green, Olivier, Crawleys, Penn, & Sliverstein, 2005; Nuechterlein & Green, 2006). Social cognition is the capacity to perceive, interpret, and generate responses to the emotions, intentions, and dispositions of others (Green et al., 2005; Roder & Medalia, 2010).

Neurocognitive and social cognitive deficits appear early and remain stable during the illness (Fioravanti et al., 2012; Green et al., 2012; Roder & Mueller, 2008; Sachs, 2008). 75%-90% of people with schizophrenia show cognitive dysfunctions, which are present in the prodromal phase, during an acute episode, in the remission and during the whole life (Bell et al., 2013; Green et al., 2012; Roder & Mueller, 2008; Sachs, 2008; Ventura et al., 2013). Neurocognitive domains are linked to functional outcome and these connections are strongly mediated by social cognition as well as negative symptoms (Schmidt, Mueller, & Roder, 2011).

Negative symptoms are divided in primary and secondary. Primary negative symptoms are schizophrenia intrinsic, whether secondary negative symptoms are the consequence of positive symptoms, depression, side effects of the medication, substance abuse and of social deprivation and have a negative impact on the patients with schizophrenia (Buchanan, 2007; Kaiser et al., 2017; Kirschner, Aleman, & Kaieser, 2017).

The lifetime prevalence of schizophrenia ranges between 0.3%-0.7%. Negative symptoms, a longer duration of illness and a poorer outcome show higher incidence rates for males (APA, 2013). Schizophrenia is a low prevalence disorder, but the burden of the disorder is great (Charlson et al., 2018).

The onset for the first psychotic episode is in the early to mid 20s for males and in late 20s for females. The onset is abrupt or slow and half of these people show depressive symptoms. An onset in earlier age is associated with a negative prognosis. The onset of schizophrenia after the age of 40 years old is presented by females, who have been married. The characteristics for schizophrenia are the same for the children, but it is more complex to give such a diagnosis. 20% of the persons with schizophrenia show a positive development, whereas a small number of them recover completely. Most of the individuals with schizophrenia are chronically vulnerable, with exacerbations and remissions of symptoms, whereas others show a progressive deterioration. Psychotic symptoms decrease over the life, negative symptoms tend to be more persistent and cognitive symptoms may not be improved during the life of the persons with schizophrenia (APA, 2013).

Individuals with schizophrenia show high comorbidity with substance related disorders, such as tobacco use disorder, with anxiety disorders, such as panic disorder and obsessive compulsive disorder and with medical conditions, such weight gain, diabetes, cardiovascular disease and metabolic syndrome, which increases the morbidity risk (APA, 2013, Tsai & Rosenheck, 2013).

5-6% die by suicide, 20% attempt suicide frequently and most of them have a significant suicidal ideation over the life time. The suicidal risk is high for all the persons with schizophrenia during the life and especially for young males with comorbid substance use. Other risk factors are having depressive symptoms, hopelessness, unemployment and the period after a psychotic episode or hospital discharge. Lastly, psychosocial dysfunction present a stable problem for these persons (APA, 2013). The assessment of suicidal ideation should take into consideration metacognitions about the probability and the consequences of loosing mental control (Hutton, Rienzo, Turkington, Spencer, & Taylor, 2018).

A differential diagnosis is important during the diagnostic process. It must be made from major depression or bipolar disorder with psychotic or catatonic features, from schizoaffective disorder, from schizophreniform disorder and brief psychotic disorder, from delusional disorder, from schizotypal personality disorder, obsessive-compulsive disorder and body dysmorphic disorder, from posttraumatic stress disorder, from autism spectrum disorders and communication disorders and lastly, from other mental disorders associated with a psychotic episode (APA, 2013).

1. 2. Treatment-Resistant Schizophrenia (TRS)

The Treatment-Resistant Schizophrenia (TRS) has been defined by the international Psychopharmacology Algorithm Project (IPAP) as: (1) no period of good functioning in the previous five years, (2) prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4–6 weeks each at doses 400-mg, equivalent of chlorpromazine or 5 mg/day risperidone, and (3) moderate to severe psychopathology, especially positive symptoms: conceptual disorganization, suspiciousness, delusions, or

hallucinatory behavior. The IPAP considers continued negative or cognitive symptoms, violence, suicidality, and recurrent mood symptoms as elements of treatment refractoriness. About 30–60% of the patients with schizophrenia belong to the TRS category (Ballon & Lieberman, 2010). Howes et al. (2017) present a very interesting review regarding a new initiative for a definition of TRS.

Patients with treatment resistant show more resistant cognitive symptoms than individuals with nontreatment resistant schizophrenia (NTRS) that are associated to clinical symptoms, as well as to high anticholinergic effects because of antipsychotic treatment (Frydecka, Beszlej, Goscimski, Kiejna, & Misiak, 2016). Psychological therapy in combination with medication is very important for individuals with TRS (Citrome, 2011). Individuals with medication-resistant psychosis have poorer prognoses, increased hospitalization, and the cost of their care is higher (Burns, Erickson, & Brenner, 2014).

1. 3. Therapeutic relationship with individuals with schizophrenia

The importance of the therapeutic relationship for the treatment of schizophrenia is great having a positive impact on the pharmacotherapy, psychotherapy and rehabilitation of persons with schizophrenia.

The relationship of therapeutic alliance and outcome is robust (Flückiger, Del Re, Wampold, Symonds, & Horvath, 2012). Therapeutic alliance presents an important element having a positive impact on cognition and functioning (Cella & Wykes, 2019).

The main strategies of building and maintaining a therapeutic relationship in CBT are normalizing and validating. Normalizing refers to the fact that other people have also similar experiences. Validation means that patient and therapist do not discuss about the truth of a delusional belief or a voice, but try to understand the emotional and behavioral reactions of the patient toward this belief or the voice and showing more empathy (Lincoln, 2006).

A motive-oriented therapeutic relationship with people with schizophrenia helps therapists to present a problematic behaviour in an unproblematic way understanding the motives of the persons with schizophrenia (Westermann, Cavelti, Heibach, & Caspar, 2015).

A good therapeutic relationship is related to better adherence to medication of the individuals with schizophrenia (Mc Cabe et al., 2012). More recovery orientation, less self stigma and more insight are independently related to a better quality of the therapeutic alliance. Clinical symptoms, adult attachments style, duration of treatment and age are not related with the quality of the therapeutic alliance. Stigma, Insight and recovery should be major issues in therapies (Kvrgic, Calveti, Beck, Rüsch, & Vauth, 2013). The above issues highlight the importance of building an appropriate therapeutic relationship and alliance with persons with schizophrenia as well as the availability of recovery oriented psychotherapies, which have a positive impact on the quality of the therapeutic alliance.

1. 4. Role of the motivation for the treatment of individuals with schizophrenia

The possibilities of participating in a therapy program are higher for the individuals with schizophrenia, when the intrinsic motivation is high. That means that the person evaluates the fact that there is a personal choice for the participation in this therapy along with positive self efficacy cognitions (Medalia & Choi, 2010; Medalia & Sapperstein, 2011). When the intrinsic motivation is very low, then therapeutic interventions to increase the motivation are necessary, such as the motivational interview (Miller & Rollnick, 2002), before the participation in a therapy.

1. 5. Treatment of schizophrenia

The main therapy for individuals with schizophrenia is the evidence based pharmacotherapy, which contribution to the improvement of psychopathology, cognition and functional outcome is not to be doubted (Huhn et al., 2019; Leucht et al., 2013; NICE, 2019; Taipale, Mehtälä, Tanskanen, & Tiihonen, 2018; Tandon, 2011). Pharmacotherapy showed unsatisfactory improvements regarding cognition and negative symptoms (Fernandez-Sotos et al., 2018; Kucharksa-Pietura & Mortimer, 2013; Tandon, 2011). Evidence based psychotherapy and rehabilitation presents an important adjunct to pharmacotherapy and plays a crucial role regarding the improvement of cognition, psychopathology and functional outcome (Buonoccore et al., 2018; Klingberg et al., 2011; Mueser, Deavers, Penn, Cassisi, 2013; Pfammater, Junghan, NICE, 2019; Roder, Brenner, & Kienzle, 2008; Roder, Brenner, Kienzle, & Spaulding, 2010; Roder, Mueller, & Schmidt, 2011; Wykes, Huddy, Cellard, McGurk, Czoboor, 2011; Wykes, Steel, Everitt, & Tarrier, 2008).

In other words, a multimodal treatment for individuals with schizophrenia enhances the recovery process and the reintegration of these people into society.

1. 5. 1. Definition of the Recovery Process

The main goal all of the evidence based treatments of individuals with schizophrenia is the recovery process, which is achieved through the improvement of neurocognition, social cognition, psychopathology and functional outcome.

There are two viewpoints pertaining to the recovery process. The first point of view is the recovery "from" schizophrenia (recovery as an outcome); which is the point of view of the experts (Remission Working Group), which means that the person is free from psychopathology and functions very well in the community in the long term. The Presidents New Freedom Commission final report, which introduces the standpoint of the recovery of patients with schizophrenia and their families, describes the "being" in the recovery process (recovery as a process). The American Psychiatric Association accepts the recovery process, which is associated with the patient's autonomy, dignity, integration in the community and the resumption of a normal development. (Amering & Schmolke, 2009; Bellack, 2006; Chan, Mak, & Chio, 2018; Davidson, Schmutte, & Dinzeo, 2008; Frese, Knight, & Saks, 2009; Jose, Lalitha & Gandhi, 2015).

The above two definitions—recovery as an outcome (recovery from illness) and recovery as a process (being in recovery) (Davidson & Roe, 2007)—can be further categorized regarding the person who is responsible for the recovery process. Recovery as an outcome depends on the evaluation of an expert (for example, rating of the symptoms) and is called objective recovery. Recovery as a process— called subjective recovery—depends on the subjective experiences of the person suffering from a mental

health illness. Objective recovery is the result of a therapy, which leads to remission of the symptoms and recovery regarding the functional outcome.

Subjective recovery, on the other side, is a personal recovery, which can be different for every person. Objective and subjective recovery are related, and emotional distress is associated with subjective appraisals of recovery (Leonhardt et al., 2017). Greater subjective recovery is associated with a better quality of life, despite the manifestation of positive symptoms (Kukla, Lysaker, & Roe, 2014). Last, cure, illness management, and personal recovery present another model of recovery (Leonhardt et al., 2017).

1. 5. 2. Recovery programs

The Illness Management and Recovery program (IMR) has been proved to be effective in the improvement of the management of the disorder, enhancing the knowledge of the disorder, and reaching important personal goals (Dalum et al., 2018; Färdig, Lewander, & Melin, 2011; Hasson-Ohayon, Roe, & Kravetz, 2007; McQuire, Kukla, & Green, 2014; Mueser, Meyer, & Penn, 2006; Salyers, Godfrey, & Mcquire, 2009)

The Wellness Recovery and Action Planning Program (WRAP) shows greater reduction in symptoms and higher improvement in hopefulness and the quality of life (Cook et al., 2012).

1. 5. 3. Cognitive behavioral therapy

CBT is the psychotherapy of choice for the individuals with schizophrenia (Mueser et al., 2013; NICE, 2019; Pfammater et al., 2006). CBT improves positive, negative symptoms, mood disorders and functional outcome. Its contribution to the recovery process of individuals with schizophrenia is very important (Beck, Rector, & Stolar, 2009; Burns, Erickson, & Brenner, 2014; Candida et al., 2016; Hofmann, Asnaani, & Vonk, 2012; Johnson & Hoffart, 2018; Kern, Glynn, Horan, & Marder, 2009; Kingdton & Turkington, 2019; Lincoln & Peters, 2019; Medalia, Beck, & Grant, 2019; Mueser et al., 2013). Additionally, CBT is effective in TRS (Burns et al., 2014; Morrison, Pyle, & Gumley, 2018).

On the other hand, CBT did not demonstrate encouraging results according to recently published meta analyses (Jahuar, McKenna, & Radua, 2014; Kennedy & Xyrichis, 2017; Laws, Darlington, & Kondel, 2018; Newton-Howes & Wood, 2013; Sarin, Wallin, & Widerlöv, 2011).

Recovery-focused CBT interventions seem to be more effective (Grant, Reisweber, Luther, Brinen, & Beck, 2014; Grant, Bredemeier, & Beck, 2017; Lysaker, Hamm, Hasson-Ohayson, Pattison, & Leonhardt, 2018; Mueser et al., 2013; Nowak, Sabariego, & Switaj, 2016).

1. 5. 4. Meta cognitive approaches

Meta cognition is an essential key element for cognitive remediation (Cella, Reeder, & Wykes, 2015) and recovery (Bonfils, Luther, & Georg, 2016; Lysaker et al., 2018; Lysaker, Gagen, Moritz, & Schweitzer, 2018a). Metacognitive Therapy (MCT), Metacognitive Training (MCTR), Metacognitive Interpersonal Therapy for Psychosis (MIT-P) and Metacognitive Reflection and Insight Therapy (MERIT) present effective and highly acceptable treatments (De Jong, Van Donkersgoed, & Timmerman 2018; Eichner & Berna, 2016; Lysaker & Klion, 2017; Lysaker et al., 2018; Lysaker et al., 2018a; Moritz, Woodward, & Balzan, 2016).

1. 5. 5. Rehabilitation programs

Evidence based rehabilitation programs are nowadays available for the scientific community focusing on the improvement of cognition, symptoms and functional outcome, which highlights their contribution to the recovery process of persons with schizophrenia (Cella & Wykes, 2019; Fiszdon & Reedy, 2012; Grant, Lawrence, Preti, Wykes, & Cella, 2017a; Kurtz & Richardson, 2012; Kurtz, Mueser, Thime, Corbera, & Wexler, 2015; Mueller, Schmidt, & Roder, 2013; Roder & Medalia, 2010; Roder et al., 2011; Tan, Lee, & Lee, 2018; Twamley et al., 2019; Ventura et al., 2019; Vita & Barlati, 2018; Wykes, et al., 2011).

Targeted cognitive interventions improve one cognitive domain, comprehensive cognitive interventions improve more cognitive domains without another psychosocial intervention, whereas broad-based interventions improve more cognitive domains in combination with other psychosocial interventions (Fiszdon & Reedy, 2012; Roder & Medalia, 2010). Broad based or integrated programs offer better results in functioning (distal outcomes) (Bowie, McGurk, Mausbach, Patterson, & Harvey, 2012; Roder et al., 2011).

The combination of CBT and rehabilitation presents an important intervention, which enhances more intensively the recovery process (Klingberg et al., 2011; Kukla et al., 2014). Psychotherapy with people with schizophrenia should be recovery oriented (Grant, Bredemeier, & Beck, 2017).

1. 5. 6. Similarities and differences between the evidence based psychotherapeutic treatments

The following conclusions can be drawn from the comparison of CR, CBT, MCT, MCTR, MIT-P, and MERIT:

CR improves cognitive deficits (neurocognition and social cognition), which enhances the improvement of symptoms and functional outcome (Wykes et al., 2011; Roder et al., 2011), whereas CBT aims to modify the content of the thoughts (Beck et al., 2009; Medalia, Beck, & Grant, 2019). MCT changes how patients react to their thoughts and focuses on dysfunctional coping strategies, such as worry and thought suppression (Johnson & Hoffart, 2018; Moritz, Lysaker, Hofmann, & Hautzinger, 2018; Moritz, Woodward, & Balzan, 2016; Lysaker, Pattison, Leonhardt, Phelps, & Vohs, 2018b),

whereas MERIT activates the four domains of metacognition: self-reflectivity, understanding the other's mind, decentration, and mastery. This leads to an improved integrated sense of self and others, which enhances the personal recovery process (de Jong et al., 2018; Lysaker et al., 2018; Lysaker & Klion, 2017).

MCTR focuses on the cognitive biases (jumping to conclusions, attributional biases, and overconfidence in distortions), which are associated with the delusions, implementing CR, CBT, and psycho education in combination. MIT-P is an adaptation of Metacognitive Interpersonal Therapy (MIT) for psychosis and focuses on the modification of interpersonal schemas and metacognitive deficits in the personality (Lysaker, Gagen, Moritz, & Schweitzer, 2018a). All these evidence-based psychotherapies focus on the cognitive information processing and functioning. CR and MCTTR contain both the element of the rehabilitation of cognitive functions. MIT-P and MERIT focus both on the impact of metacognitive deficits on the disconnection from the interpersonal schemas.

On the other hand, there are differences between the above interventions: CR is concentrated on the improvement of neuro- and social cognition, although the integrated programs, such as IPT, focus also on the improvement of social problem-solving competence, which is called behavioral interventions. CBT, MCT, and MERIT focus on cognitive interventions. CBT is concentrated on how to change the content of the thoughts, whereas MCT focuses on what the persons think about their cognitions or thoughts. MERIT enhances the synthesis of information about self and others. MCTTR is a combination of rehabilitation and CBT, and lastly, MIT-P focuses on the schemas of the personality.

The combination of CBT, rehabilitation programs, recovery programs and meta cognitive approaches should be a major goal in research and clinical praxis.

1. 5. 7. The Integrated Psychological Therapy

Integrated Psychological Therapy (IPT) is one of the most evaluated integrated therapies for individuals with schizophrenia in Europe and internationally (Aloi et al., 2018; Obeid, Hallit, Sacre, & Kazour, 2019; Mueller et al., 2013; Roder et al., 2011; Ruiz-Iriondo, Salaberia, Polo-Lopez, Iruin, & Echebura, 2019).

IPT is a manualized rehabilitation program and a group cognitive behavioral therapy approach, which integrates interventions in neurocognition, in social cognition and social functions in one therapy concept. Its concept is based on the assumption, that cognitive deficits have a pervasive effect on higher levels of behavioral organization, such as social functioning. IPT is divided into 5 subprograms with increasing levels of complexity and emotional distress.

It begins with neurocognition (SP 1: Cognitive Differentiation) and social cognition (SP2: Social Perception), followed by intervention on communication skills (SP3: verbal communication), social skills (SP4) and interpersonal problem solving skills (SP5). The 5 subprograms should be applied sequentially, but they have been administered also separately in research and practice. A manual of IPT is available (Roder, Brenner, & Kienzle, 2008). It is translated in 13 languages (Roder, Mueller, Brenner, & Spaulding, 2010; Roder et al., 2011) as well as in Greek (Roder, Brenner, Kienzle, & Efthimiou, 2007). The Greek translation presents an adaptation of the program in Greek language and Greek mentality (Roder et al., 2007).

Cognitive Differentiation (SP1) leads to improvement of cognitive functions and consists of the following levels: level 1: exercises with cards, level 2: verbal conceptual systems (Synonyms, antonyms, word definitions, word cards, concepts with different meaning depending on the context).

Social cognition (SP2) improves social perception and visual perception of social situations. It is with photos (slides) implemented and consists of 3 levels (level 1: Information, level 2: Interpretation and discussion, level 3: title of the photo) (Roder et al., 2008).

Verbal communication (SP3) improves the training of three basic communication abilities: Hear, understand and react and consists of 5 levels (level 1: spatial reproduction of given sentences, level 2: analogous reproduction of self-phrased sentences, level 3: self-phrased W-Questions with reaction, level 4: The group make questions to one or two members of the group regarding an issue and level 5: free communication). Verbal communication presents a bridge between the cognitive part of the IPT (SP1, SP2) and the second part with social skills and problem solving (Roder et al., 2008).

Social skills (SP4) improves social competence and consists of the following levels (level 1: cognitive working up of a social situation, level 2: implementation with role play) (Roder et al., 2008).

Lastly, interpersonal problem solving (SP5) improves the problem perception and the ability of problem solving and consists of the following levels: (Level 1: Identification and analysis of a problem, level 2: cognitive problem working up, level 3: alternatives of solutions,

level 4: discussion of the alternatives of the solutions, level 5: decision for a solution, level 6: implementation in praxis, level 7: feedback for success or not) (Roder et al., 2008).

Anxiety, motivation and activity must be associated with the structure of the group procedure. The group's works ideally, when anxiety is low, activity is middle and the structure is optimal. There are many therapeutic strategies, which increase structure, such as calling group members with their names, repeating the answers of the members or setting rules for the group. All the above issues increase the motivation of the patients to participate in the therapy (Roder et al., 2008).

The IPT concept is finally associated with integrated models of functioning (please see Figure 1 and 2). The improvement of neurocognition, social cognition, treatment orientation, negative symptoms and positive symptoms lead to functional recovery. Neurocognition is linked to functional outcome and this connection is strongly mediated by social cognition as well as negative symptoms. Negative symptoms interact with treatment orientation and cognition. Positive symptoms are independent (Green et al., 2008; Roder et al., 2010).

Figure 1: Schematic presentation of the five subprograms

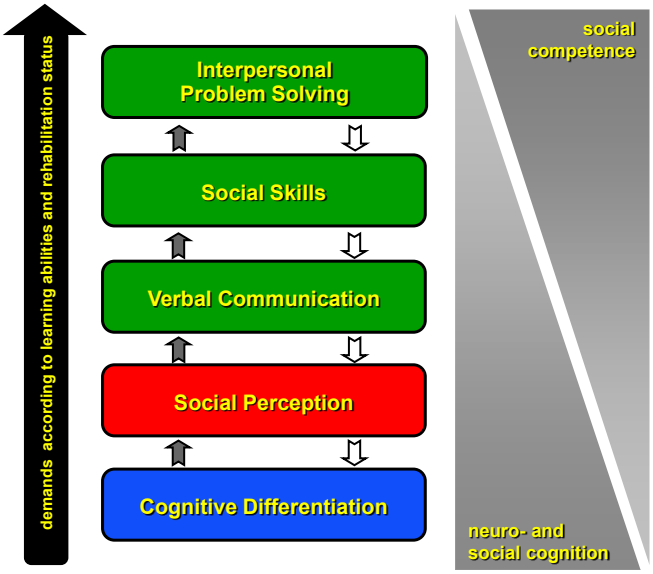
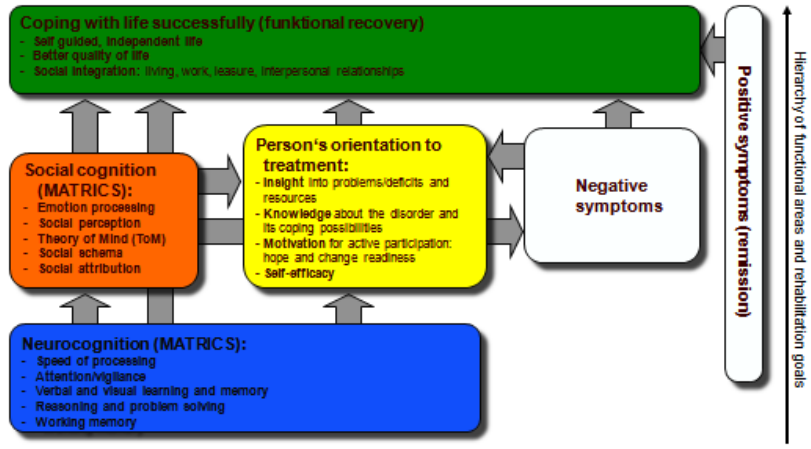


Fig. 1 Schematic presentation of the five IPT subprograms

Figure 2: Integratives Model von Rehabilitation



Integratives Model von Rehabilitation (Roder et al., 2010, Mueller, 2012)

The implementation of all 5 subprograms is recommended and produces better results in distal outcomes, because IPT generates better synergestic effects and improves functional outcome (Roder et al., 2011).

Meta analysis regarding the efficacy of IPT are available (Mueller et al., 2013; Roder et al., 2011). 36 Studies with 1601 individuals with schizophrenia were included in the meta analysis. IPT showed better results in all the proximal and distal outcomes (neurocognition, social cognition, negative symptoms and functional outcome) in comparison to the control group (Placebo and TAU). These positive results were maintained in the follow up after 8. 1. months. When all 5 subprograms are implemented, IPT shows better results in distal outcomes (negative symptoms and functional outcome) (Roder et al., 2011).

The IPT studies were conducted in Germany, in Switzerland, in Austria, in Italy, in Spain, in Norway, in the Netherlands, in the USA, in Japan, in Canada, in Panama and in Brazil. IPT is an efficacious and effective rehabilitation program and robust across sample characteristics and treatment conditions (Roder et al., 2011).

15 IPT studies with 632 Patients were included in another meta analysis. The hypothesis was, whether IPT is effective in younger patients (<40) or in middle-aged patients (>40) and whether the control group (TAU or unspecific group activities) showed changes in results depending on age. IPT showed significant medium to large effect sizes independent on age for the global cognitive score, for neurocognition, for social cognition, for psychopathology, for functional outcome and for the total therapy effect.

The IPT effects for middle aged patients were larger in global cognitive score, in neurocognition and in social cognition in comparison to the effects of younger patients. Opposite results showed the control group. The results provide evidence for the efficacy of IPT independent on age (Mueller et al., 2013).

2. Background of this dissertation thesis

IPT is an European integrative evidence based rehabilitation program and one of the most evaluated therapies for individuals with schizophrenia (Mueller et al., 2013; Roder et al., 2008, 2010, 2011; Roder & Medalia, 2010). Those were important criteria for our research group in Athens, in order to choose IPT as one potential therapy to be implemented in Greek patients with schizophrenia.

Our research group (Stavroula Rakitzi, Konstantinos Efthimiou†, Polyxeni Georgila) was grounded in 2006. We had contacts with the Berner Group (Prof. H. D. Brenner & Prof. V. Roder), in order to build a cooperation with them, so that IPT could be implemented in Greece. The Greek manual of IPT was translated and published from our Group in 2007 (Roder et al., 2007). A research protocol regarding an implementation of IPT in a Greek sample of individuals with schizophrenia at the adult psychiatric department of the General Hospital G. Gennimatas in Athens for the first time in Greece, was approved from the scientific committee of the hospital and was implemented between 2008-2013.

A two day conference was organized from our Group in 2009, in cooperation with the adult psychiatric department of the General Hospital G. Gennimatas and the Institute of Behavior Research and Therapy, in which the experience of the adult psychiatric department of the General Hospital G. Gennimatas as well as a pilot study regarding the efficacy of IPT in a small group of patients were presented.

The above research protocol was a cooperation between the Instititute of Behavioral Research and Therapy (Stavroula Rakitzi & Konstantinos Efthimiou), the adult Psychiatric Department of the General Hospital G. Gennimatas (Polyxeni Georgila) and the University Psychiatric Clinic in Bern in Switzerland (Prof. V. Roder).

Konstantinos Efthimiou was a supervisor for the implementation of IPT in the psychiatric department. Polyxeni Georgila was responsible for the patients, who participated in this project and for the implementation of IPT in this psychiatric department. Stavroula Rakitzi was responsible for this research protocol and for the implementation of IPT in this clinic and coordinated everything in cooperation with the other members of the group and with Prof. Volker Roder. The aim of this research protocol was to take empirical data regarding the efficacy of IPT in Greek individuals with schizophrenia and to develop a trainings program in IPT for psychologists and psychiatrists in Greece, who are trained in Cognitive Behavioral Therapy. This trainings program was offered between 2012-2017 from the Association for Cognitive Behavioural Studies in CBT in cooperation with the Institute of Behavioral Research and Therapy. A Greek edition (Book) about the evidence based interventions for individuals with schizophrenia (Rakitzi, Georgila & Efthimiou, 2016), in which the history of IPT in Greece is also presented amongst other things, was published in 2016 from our group.

Our colleague Konstantinos Efthimiou died unfortunately in September 2017 and since then the trainings program to IPT is offered from Stavroula Rakitzi and Polyxeni Georgila in private practice. Our empirical data were presented in symposia and workshops in various national and international conferences in Athens and in other countries between 2009-2018.

Paper 1 (Rakitzi, Georgila, Efthimiou, Mueller, 2016) and paper 2 (Rakitzi & Georgila, 2019) came from the above research protocol. Paper 3 (Rakitzi et al., 2020) was developed after this research protocol. The above research initiative aimed to present empirical data regarding the efficacy of IPT in Greece, regarding the efficacy of IPT in NTRS and TRS and to display the importance of evidence-based psychotherapy for persons with schizophrenia.

3. Papers submitted as part of this dissertation thesis

Paper 1: Rakitzi, S., Georgila, P., Efthimiou, K., & Mueller, D. R. (2016). Efficacy and feasibility of the Integrated Psychological Therapy in Greece: Final results of an RCT. *Psychiatry Research, 242,* 137-143. http://dx.doi.org/10.1016/j.psychres.2016.05.039

3. 1. Abstract

The goal of this study was to evaluate the efficacy and feasibility of the Integrated Psychological Therapy (IPT) in Greece. For this purpose, the cognitive part of the IPT was compared in a RCTs with TAU. 48 individuals with schizophrenia took part in this study. Significant effects favoring IPT were found for proximal outcomes (working memory, social cognition) and for distal outcomes (negative symptoms, insight, general psychopathology). Significant effects favoring TAU were found in quality of life. This study supports evidence for the efficacy and feasibility of IPT in Greece. The importance of the above paper focuses on the first study internationally regarding the efficacy of IPT in a Greek sample, which is in accordance with the meta analysis for IPT (Mueller et al., 2013; Roder et al., 2011). The above hypotheses were answered through the published RCT (Rakitzi et al., 2016).

3. 1. 2. Introduction

75-90% of people with schizophrenia suffer from cognitive deficits (Bell et al., 2013; Fioravanti et al., 2012). The following cognitive domains were initially recognized by the Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS): neurocognition: speed of processing, attention/vigilance, verbal and visual memory, reasoning and problem solving, social cognition: emotion processing, social perception, Theory of Mind (TOM), social schema, attribution (Nuechterlein & Green, 2006).

Pharmacological agents show only small effects in improving cognitive domains (Leucht et al., 2013). Cognitive Remediation Therapy (CRT) improve directly cognitive functions, which is supported in Meta-analyses (Kurtz & Richardson, 2012; Wykes et al., 2011). Integrated approaches combining CRT with other therapy topics are more successful regarding the improvement of distal outcomes (Roder et al., 2011; Wykes et al., 2011).

The international recognition of a European evidence based integrated rehabilitation program was an important criterion for this research project, in order to be chosen to be implemented in Greece. The above paper (Rakitzi, Georgila, Efthimiou, & Mueller, 2016) presents the first empirical study in Greece, which aimed to present first results regarding the implementation and efficacy of IPT in Greece (Rakitzi et al., 2016).

The aim of this study was to examine the following hypothesis: The IPT group shows better improvement in proximal outcome of neurocognitive and social cognitive functions and in distal outcomes of psychopathology and functional outcome-in comparison to TAU.

3. 1. 3. Material and Methods

3. 1. 3. 1. Study population

48 patients with schizophrenia were recruited from the outpatients department of the General Hospital G. Gennimatas in Athens Greece, one of the biggest General Hospitals in Greece. All persons were initially invited from the Director of the clinic for an interview, in which the research project was presented. The advantages and disadvantages of participating in this study were discussed in individual sessions with the patients and their families, separately. The patients have given informed consent to participate in the project. The patients were not paid for the participation. The study protocol was approved from the Scientific Committee of the General Hospital G. Gennimatas. Changes in medication were allowed before the study intake. The medication was controlled during the whole therapy at monthly sessions with the psychiatrists. The medication did not change during the project. Finally, the following inclusion criteria were used: IQ>80, Age between 20-50 years old, the duration was more than two years, no excessive substance abuse, no brain disease and no relapse 2 months before the study entry.

3. 1. 3. 2. Study design

This study summarized a randomized controlled trial (RCT). The cognitive part of IPT was compared to treatment as usual (TAU). After a baseline assessment (T1), a randomization procedure took place: Patients were allocated the IPT group as experimental group and treatment as usual as the control group using a random drawing of lots by an independent person. The second assessment was carried out after 10 weeks intervention.

The third and final assessment was carried out at a follow up of three months after the end of the therapy. TAU was chosen for the control group because there were no additional therapists for another control condition. This study is the first RCT study in Greece. TAU is recommended as a necessary first step in evaluating the efficacy of IPT.

3. 1. 3. 3. Therapists

A psychologist was the main therapist and a psychiatrist the co-therapist. Both are experienced psychotherapists and well educated in IPT procedure. One blinded rater with an M. D. degree, not participating in the study, conducted the assessments.

3. 1. 3. 4. Intervention

The experimental group is a cognitive remediation group therapy following the cognitive part of IPT. This consisted completion of the two first subprograms of "Cognitive Differentiation" and "Social Perception" along with the first two levels of the third subprogram "Verbal communication". IPT received 20 biweekly therapy sessions over 10 weeks, in addition to TAU and each session lasted 60 min., in accordance with the guidelines of the author's recommendation for the implementation of the cognitive part of IPT (Roder et al., 2008; 2010; 2011).

TAU is defined as standard medication, case management and individual supportive therapy by a psychiatrist or a psychologist. Supportive therapy included non specific intervention, which helped the outpatients to cope with the problems in daily routine. It did not contain specific cognitive behavioral techniques.

The TAU group received the same therapy as IPT regarding the intensity of the therapy. Each of the group consisted of 8 participants. 3 IPT and 3 TAU groups took part. An attendance rate of less than 50% was defined as drop out and was excluded from the analysis.

3. 1. 3. 5. Measures

3. 1. 3. 5. 1. Cognition (proximal outcome)

The neurocognitive domain of vigilance/attention was evaluated with the continuous performance test (Mass, 2002). The neurocognitive domain of working memory was evaluated with the Letter Number Span (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Nuechterlein & Green, 2006), using the Greek translation (Rakitzi et al., 2007a). The neurocognitive domain of verbal memory was evaluated with Greek verbal memory test (VMT) (Vlahou et al., 2013).

Lastly, the social cognitive domain of social perception was evaluated with the Social Perception Scale (SPS) (Garcia, Fuentes, Ruiz, Gallach, & Roder, 2003; Ruiz, Garcia, Fuentes, Garcia-Merita, 2005), using the Greek translation of SPS (Rakitzi et al., 2007b).

3. 1. 3. 5. 2. Psychopathology (distal outcome)

Positive, negative and general symptoms were assessed using the Greek version of the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987; Lykouras, Botsis, & Oulis, 2005). A well-experienced and blinded rater (M. D.) conducted the PANSS interview.

3. 1. 5. 3. Functional outcome (distal outcome)

Quality of life was assessed using the Greek version of the World Health Organization Quality of Life WHOQOL (Ginnieri-Kokkosis, Triantafillou, Antonopoulou, Tomaras, Christodoulou, et al., 2003; Ginnieri-Kokkosis, Triantafillou, Tomaras, Soldatos, Mavreas, Christodoulou, 2012). Psychosocial functioning was assessed using the Global Assessment and Functioning Scale GAF (American Psychiatric Association, 2004). GAF and PANSS were conducted from the same blinded rater.

3. 1. 6. Data analysis

The SPSS Version 21 has been used for statistical analysis. The General linear model for repeated measurements (GLM) and t-test were chosen to treat analysis of the empirical data (Bortz & Döring, 2002). Additionally, effect sizes were calculated using the difference between the mean scores of the comparison groups divided by the pooled standard deviation (Cohen, 1988). The sample size estimation was there for based on the predicted large effect sizes for GLM for repeated measurements (f=0.4) and for t-tests(d=0.8), and for pearson correlation coefficient (r=0.5) with a generally accepted statistical power of 0.80 at an alpha level of significance of 5% (Cohen, 1988). Effect sizes can be generally categorized into small (d=0.2), medium (d=0.5), and large (d=0.8). However, the sample size is underpowered to identify medium or small effect sizes.

3. 1. 7. Results

Figure 3: Flow diagram of the IPT study

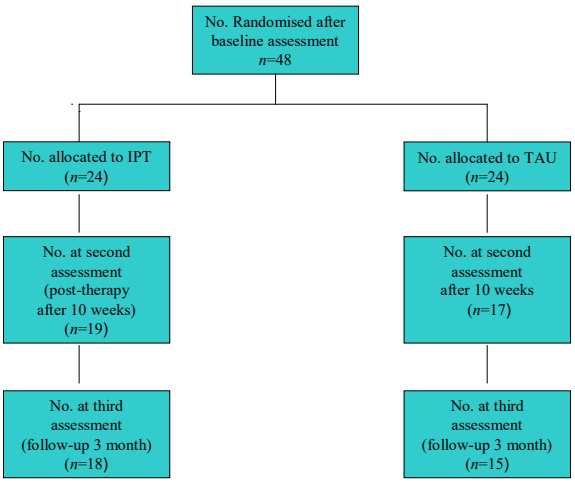


Fig. 3 Consort diagram: Flow diagram of subject progress through phases of the randomized controlled trial for the Integrated Psychological Therapy (IPT) and Treatment As Usual (TAU) group.

IPT and the control group each included 24 outpatients with schizophrenia (Fig. 3). 6 patients of the IPT group (25%) and 9 of the control group (37.5%) dropped out (chi-square=0.87, p=0.35). The patients who dropped out did not differ in any patient characteristics or baseline assessments from those who finished the study participation ($t<1.5$; $p>0.14$). The reasons for dropping out were low motivation (IPT: n=5; TAU: n=5) to follow through this project (attendance rate 50%) or relapse (IPT: n=1; TAU: n=4). The two comparison groups are near identical regarding patient characteristics (Table 1). There was no significant difference regarding age, intelligence assessed by Wechsler Adult Intelligence Scale (WAIS, Aster et al., 2006), sex, medication and duration of illness.

Table 1: Patient characteristics (N=48) of the IPT study

	IPT **N=24** **M (SD)**	**TAU** **N=24** **M (SD)**	***t/Chi.Sq***	***p***
Age	31.3 (7.2)	33.8 (6.7)	1.2	0.22
IQ (WAIS[a])	89.9 (9.4)	89.7 (7.7)	0.0	0.92
Duration of illness	5.4 (1.3)	(5.9) (1.1)	1.4	0.16
Medication (chlorpromazine equivalents)	542.1 (391.1)	512.1 (355.0)	0.28	0.78
Atypical (%)	83.3	83.3	0.0	1.0
Gender (% male)	67	67	0.0	1.0

[a]Wechsler Adult Intelligence Scale WAIS
.

Table 2: Proximal and distal outcome: General Linear Model (GLM) for repeated measures and effect sizes (d)

		T1	T2	T3	GLM T1-T2		Effect size T1-T2	GLM T1-T2-T3[a]		Effect size T1-T3
		M (SD)	M (SD)	M (SD)	F	*p*	*d*	F	*p*	*d*[b]
Proximal outcome										
CPT[c] commission	**IPT**	3.3 (4.2)	2.9 (7.6)	1.7 (4.1)	2.4	.13	0.68	0.39	0.48	0.39
	TAU	2.5 (3.3)	3.3 (5.0)	3.1 (5.2)						
LNS[d]	**IPT**	13.1 (4.2)	17.9 (2.4)	17.3 (4.8)	**9.0**	***.00***	0.95	**3.5**	***0.04***	0.80
	TAU	12.4 (4.49)	13.6 (4.9)	12.8 (4.5)						
VMT[e] recognition	**IPT**	14.1 (1.6)	14.7 (1.2)	14.6 (2.1)	0.4	.56	0.23	0.6	0.53	0.53
	TAU	13.1 (1.7)	13.7 (1.5)	12.4 (5.3)						
SPST[f] stimulus	**IPT**	19.6 (7.3)	41.9 (11.7)	46.3 (10.2)	**21.9**	***.00***	2.64	**31.7**	***0.00***	3.89
	TAU	15.7 (7.2)	16.1 (5.9)	14.0 (8.6)						
SPST interpretation	**IPT**	6.2 (1.1)	10.2 (1.5)	11.1 (2.2)	**27.0**	***.00***	2.50	**15.7**	***0.00***	3.18
	TAU	5.9 (1.6)	6.3 (1.4)	6.1 (2.9)						
SPST title	**IPT**	4.1 (2.1)	11.3 (1.0)	10.7 (1.7)	**48.6**	***.00***	3.24	**30.3**	***0.00***	3.18
	TAU	3.4 (2.2)	3.5 (2.8)	3.5 (2.9)						
Distal outcome										
PANSS[g] positive symptoms	**IPT**	25.9 (6.9)	20.1 (5.2)	17.6 (5.7)	2.9	.09	0.43	2.6	0.08	0.44
	TAU	27.5 (6.9)	25.2 (5.0)	21.9 (5.1)						
PANSS negative symptoms	**IPT**	33.5 (4.5)	26.1 (4.3)	24.0 (4.6)	***13.6***	***.00***	0.89	***12.0***	***0.00***	1.21
	TAU	31.0 (4.3)	30.3 (5.8)	28.9 (4.7)						
PANSS general symptoms	**IPT**	59.9 (14.3)	45.6 (9.4)	43.9 (13.8)	3.7	.06	0.62	***5.0***	***0.01***	0.75
	TAU	59.0 (12.6)	55.5 (9.9)	52.2 (13.0)						
PANSS insight	**IPT**	4.1 (1.2)	2.9 (0.9)	2.6 (0.8)	1.7	.20	0.62	1.9	0.16	0.57
	TAU	4.5 (1.2)	4.1 (1.2)	3.6 (1.1)						
GAF[h]	**IPT**	36.0 (10.9)	44.1 (11.5)	54.3 (11.8)	1.7	.20	0.28	1.9	0.16	0.50
	TAU	40.5 (15.8)	43.9 (16.2)	52.5 (17.0)						
WHOQOL[i] (overall)	**IPT**	13.5 (3.7)	14.8 (3.5)	13.4 (4.4)	0.3	.60	0.17	***4.0***	***0.03***	-0.69

TAU	13.7 (4.0)	14.8 (2.2)	16.2 (2.7)

[a]GLM pre and post therapy and follow up
[b]d: Cohen's d (positive d scores indicate superiority of the experimental group IPT)
[c]Continuous Performance Test
[d]Letter Number Span
[e]Verbal memory Test
[f]Social Perception Test
[g]Positive And Negative Syndrome Scale
[h]Global Assessment and Functioning scale
[i]World Health Organization Quality of Life
Bonferroni correction (Type I error): $\alpha'=0.004$

Baseline analysis revealed no significant differences in any outcome variable (T-test: $t<1.6$; $p>0.13$) between the two comparison groups. Regarding proximal outcome, in consistent results could be found in neurocognitive functions. IPT patients showed significant higher effects in working memory, assessed by LNS, during therapy and highly significant effects during therapy and the follow-up period when compared to the control group. However, the two groups did not differ in verbal memory (VMT) and vigilance (CPT). Regarding social cognition, IPT patients obtained generally highly significant effects in all variables concerning social perception assessed by SPS during therapy as well as during therapy and the follow-up period compared to TAU. These effects were the strongest in social perception and most robust in all assessments.

Regarding more the distal outcome, strong effects of high significance favoring IPT could be found in negative symptoms assessed by PANSS during therapy, and in negative symptoms as well as general symptoms during therapy and the follow-up period. However, no effects could be found relating to positive symptoms (PANSS) and psychosocial functioning assessed by GAF. The PANSS score of insight showed significant superiority for IPT compared to TAU both after therapy and at the follow-up. In the assessment of the quality of life (WHOQOL), a significant effect favoring TAU was found at the follow-up (Table 2).

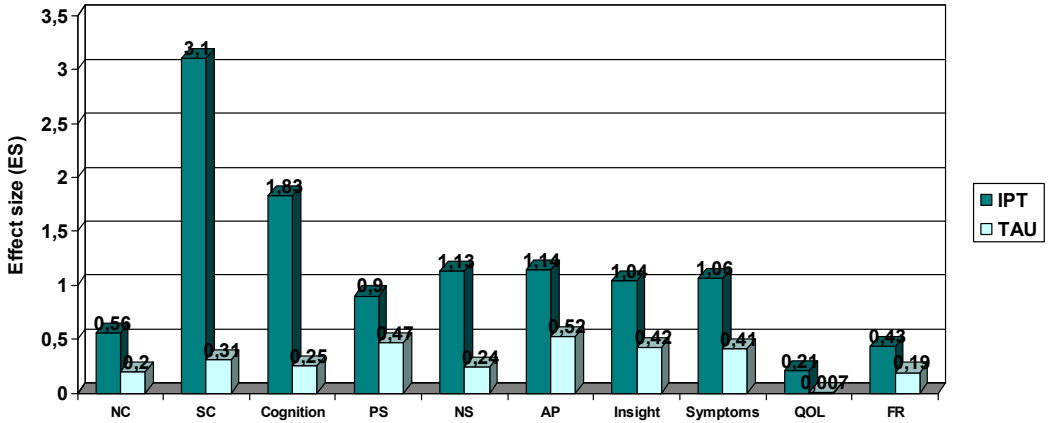
Pearson correlation coefficients between patient characteristics and change scores in outcome (T1–T2; T1–T3) were calculated to identify possible impacts on outcome. Only the duration of illness was significantly associated with an improvement in insight during therapy in IPT (r=0.49; p=0.04) suggesting that younger patients improved more than the older patients did. However, this effect was not evident at follow up and under TAU condition.

In addition, the calculation of effect sizes (d) for the therapy phase (T1–T2) and the therapy and the follow-up phase (T1–T3) between the IPT and the TAU group showed large effect sizes in working memory (LNS) and in social perception (SPS) during therapy, which were still evident at follow up. The composite scores of neurocognition (mean of all assessed variables relating to neurocognition) were d=0.62 during therapy and d=0.57 during therapy and the follow up period. Composite scores of all cognitive assessments (neuro-and social cognition) were d=1.70 during therapy and d=1.99 during therapy and the follow up.

Effect sizes of the composite score of distal outcome variables were d=0.56 during therapy and d=0.42 during therapy and follow up. The mean effect of all variables reporting the overall therapy outcome, showed a large effect size after therapy favouring IPT (d=0.95), that could be maintained at follow-up (d=0.97) (Table 2).

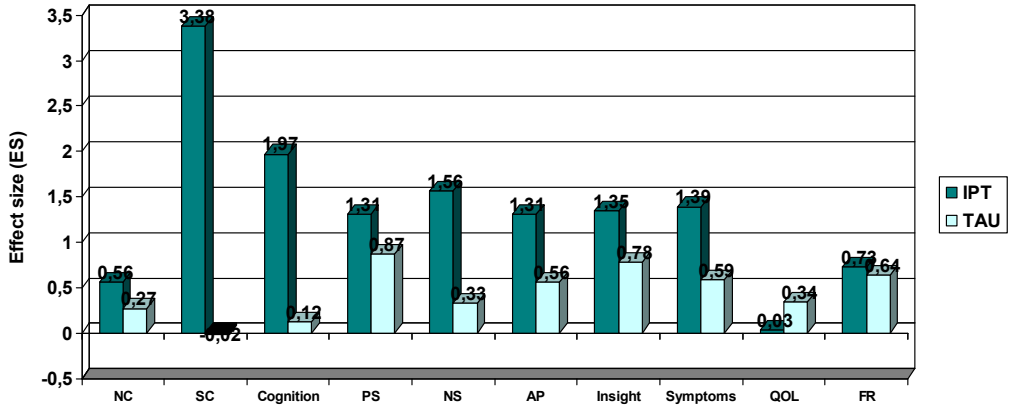
Additionally effect sizes within groups and the total therapy effect (T1-T2, T1-T3) for this dissertation thesis were calculated considering all the variables of this study and not only the variables mentioned in Table 2.

Figure 4: Effect sizes within the groups T1-T2



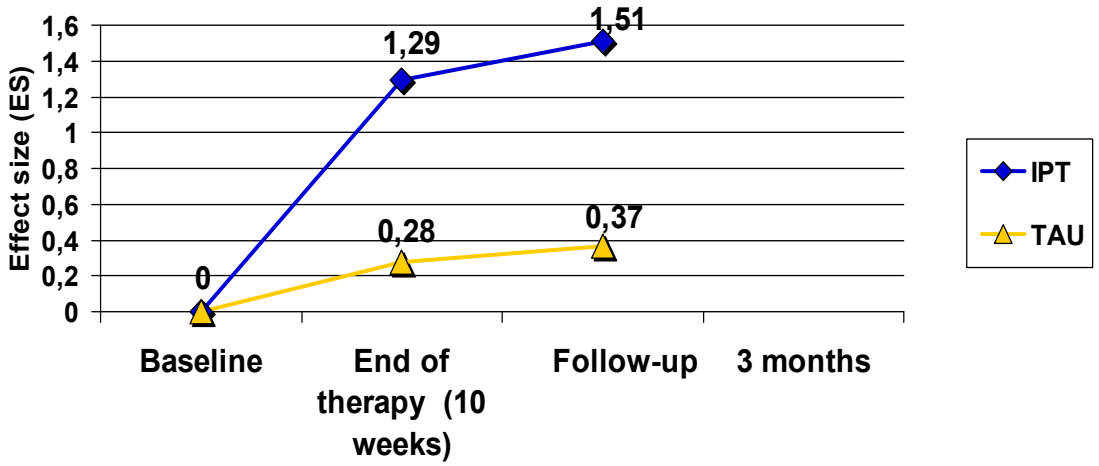
Note: NC: Neurocognition, SC: social cognition, PS: positive symptoms, NS: negative symptoms, AP: General Psychopathology, QOL: Quality of life, FR: functional recovery.

Figure 5: Effect sizes within the groups T1-T3



Note: NC: Neurocognition, SC: social cognition, PS: positive symptoms, NS: negative symptoms, AP: General Psychopathology, QOL: Quality of life, FR: functional recovery.

Figure 6: Total therapy effect size T1-T3



3. 1. 8. Discussion

This RCT represents the first efficacy study of IPT in the Greek population. This study focused exclusively on the cognitive part of IPT addressing neurocognition and social cognition. IPT groups only showed significant effects after therapy in working memory that could be maintained during follow-up, though not in verbal memory and vigilance. The positive effects in working memory are in line with the effects presented by the meta-analysis of Wykes et al., (2011), as well as the meta analysis of IPT studies (Mueller et al., 2013; Roder et al., 2011). But the effects in vigilance and verbal memory were contrary to the ones found in the above mentioned meta-analysis. Both found significant medium effects in verbal memory and vigilance. The strict outpatient setting of our study including more functional patients, may explain these results: assessment in CPT had already obtained relatively good functioning at baseline (Suwa, Matsushima, Otha, & Mori, 2004). Furthermore, the small sample size may be responsible for the fact that only large effect sizes achieved the statistical level of significance (type 2 error).

The superior effects in social perception, which were maintained during follow up, could be interpreted as the horizontal generalization of the therapy effect. The effect sizes in social perception were much higher compared to the meta-analysis on social cognitive training (Kurtz and Richardson, 2012), but reached the same level as in the evaluation study of SPS (Fuentes, Garcia, Ruiz, Soler, & Roder, 2007). The assessment of social perception (Fuentes et al., 2007) was very close to the content of the intervention. In consequence, the improvement of the IPT patients was by far the highest of the whole study.

IPT intervention significantly reduced negative symptoms, and to a lesser extent also showed reductions in other symptom dimensions after therapy and at follow up. These effects are superior to those summarized by the meta-analysis of Wykes et al., (2011), where no follow-up effects were evident.

The reduction of negative symptoms through the neuro- and social cognitive part of IPT is more important in the background of empirically-based mediator models on schizophrenia symptomatology, suggesting that neurocognitive domains are linked to functional outcome. These connections are strongly mediated by social cognitive functions as well as by negative symptoms. (Green et al., 2012; Schmidt et al., 2011). From a clinical point of view, the reduction of negative symptoms may support a better prognosis and improved social functioning, since negative symptoms are shown to have a negative impact on these issues (Klingberg et al., 2011).

However, no effects favouring IPT could be found in the GAF score and in the quality of life. Since the social subprograms of IPT were deleted from the therapy procedure, these results recommend the implementation of the whole integrated procedure of IPT. In other studies, only the combination of cognitive remediation with other goal-oriented interventions obtained effects in social functioning (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Wykes et al., 2011). In this study, patients under TAU conditions showed even better self rating in the overall quality of life, than did IPT patients after the end of the 3 month follow-up period. This may be an artefact of the assessment.

On the other hand, it may be linked with the insight of patients into the illness: poor insight has been linked to more negative attitudes toward medication, longer episodes of antipsychotic non-adherence, more frequent hospitalization, greater levels of positive and negative symptoms, lower self-esteem as well as poorer psychosocial function and quality of life (Lysaker et al., 2011). IPT patients significantly increased insight and therefore may also have developed a more realistic view of their own life, in comparison to the control group.

The total therapy effect within the groups (T1-T2; T1-T3) shows the superiority of IPT in comparison to TAU.

This study makes such context possible and attractive for further rehabilitation initiatives with IPT.

IPT could be implemented for the first time in a context of a psychiatric department of a general hospital in Greece. After the initial publication of the Greek version of IPT in 2007 (Roder et al., 2007; Efthimiou, Rakitzi, & Roder, 2009), this study now supports evidence for the feasibility of IPT procedure in patients with schizophrenia in Greece. The relatively low dropout rate and satisfying feedback by patients suggest a positive acceptance of the treatment

Limitations of the study:

1) First of all, the sample was small and only sufficient to discover large effects. The statistically under powered sample size may have led to type II (Beta) errors: we possibly would have found more significant effects in a larger sample.

2) The follow-up phase of 3 months after the end of therapy may have been too short to really identify stable generalization effects. In comparison, the mean follow-up among IPT studies is more than 8 months (Roder et al., 2011).

3) The inclusion of TAU may have been limited in controlling unspecific group effects of IPT treatment. An active control condition may have helped to identify these effects. However, IPT is a well-evaluated therapy approach. In quantitative reviews, the superiority of goal-oriented intervention of IPT compared to unspecific group therapy, is well documented (Roder et al., 2011). TAU is recommended as a necessary first step in evaluating the efficacy of IPT in the Greek population.

4) Regarding the assessments, the much in common MATRICS Consensus Cognitive Battery (MCCB) would have been a more appropriate instrument in measuring cognitive changes in these Greek patients. However to our knowledge, no Greek translation of MCCB is available yet.

5) Regarding more distal outcomes, it is a clear limitation to have assessed social functioning only by GAF. Although GAF is widely used and seems appropriate in samples of stable patients, it may be confused with symptom severity and may not be very sensitive for psychosocial changes (Mueller, Schmidt, & Roder, 2015; Robertson et al., 2013; Startup, Jackson, & Bendix, 2002). Therefore, it would have been useful to include more measures of social functioning.

6) We have only included the cognitive part of IPT in this study. To really benefit from the advantage of IPT as an integrated therapy approach in long-term treatment, it would be important to implement the complete IPT program (Roder et al., 2011).

3. 2. The Integrated Psychological Therapy and Treatment-Resistant Schizophrenia: Initial findings.

Paper 2: Rakitzi, S., & Georgila, P. (2019). The Integrated Psychological Therapy and Treatment-Resistant Schizophrenia: Initial findings. *Psychiatry,* 82 (4), 354-367, https://doi.org/10.1080/00332747.2019.1616658.

3. 2. 1. Abstract

The aim of this Randomized Controlled Trial (RCT) is to present the initial findings of a larger RCT study conducted internationally for the first time, regarding the hypothesis, when the Integrated Psychological Therapy (IPT) for individuals with schizophrenia is more and when it is less effective, regarding Treatment-Resistant Schizophrenia (TRS) and nontreatment resistant schizophrenia. Forty-eight outpatients with schizophrenia participated in this RCT study. There was a statistical significance for verbal memory; positive, negative symptoms and general psychopathology, functioning and quality of life favoring NTRS. Effect sizes showed superiority of NTRS in comparison to TRS. The sign test showed a significant improvement in Integrated Psychological Therapy treatment-resistant schizophrenia (IPTTRS) that was maintained in the follow-up, in Integrated Psychological Therapy nontreatment resistant schizophrenia (IPTNTRS) and in Treatment as Usual nontreatment resistant schizophrenia (TAUNTRS).

The IPT is more effective in NTRS in comparison to TRS, although IPTTRS showed some improvements, maintained at follow-up. Further RCT studies with larger samples are needed.

The importance of this published study (Rakitzi & Georgila, 2019) is the fact, that this is the first RCT study in Greece and internationally regarding the hypothesis, when IPT is more and when less effective in persons with schizophrenia. The above hypotheses were answered through the published RCT (Rakitzi & Georgila, 2019), which is a part of the published study (Rakitzi et al., 2016).

3. 2. 2. Introduction

30–60% of the patients with schizophrenia belong to the TRS category (Ballon & Lieberman, 2010). Patients with TRS show more resistant cognitive symptoms than individuals with nontreatment resistant schizophrenia (NTRS) that are associated to clinical symptoms, as well as to high anticholinergic effects because of antipsychotic treatment (Frydecka, Beszlej, Goscimski, Kiejna, & Misiak, 2016). Psychological therapy in combination with medication is very important for individuals with TRS (Citrome, 2011).

This paper presents the initial findings of larger study, which will be conducted in the near future by the authors. It aimed to specifically examine the following hypothesis: The IPT is more effective in NTRS in the proximal outcome of neurocognitive and social cognitive functions and in distal outcomes of symptom reduction and psychosocial functioning in comparison to TRS (IPT, TAU) group. This study will probably offer new empirical data regarding the interaction of IPT against TAU and TRS against NTRS in combination with medication.

3. 2. 3. Material and Methods

3. 2. 3. 1. Definition of TRS in this study

The TRS is operationalized in this study through the following criteria: no period of good functioning in the previous five years, prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4–6 weeks, each at doses 400-mg equivalents of chlorpromazine, persistent negative and cognitive symptoms (Ballon & Lieberman, 2010; Buchanan, 2007; Howes et al., 2017).

3. 2. 3. 2. Study population

The study was conducted with 48 Greek outpatients with schizophrenia between 2009–2013 at the psychiatric department for adults of the General Hospital "G. Gennimatas" in Athens Greece.

The methods of the study (study design, therapists, intervention, measures) is described above with details in the first published study (Rakitzi et al., 2016).

3. 2. 3. 3. Data analysis

The SPSS Version 13 was used for statistical analysis. The GLM (General Linear Model) for repeated measurements, t-test to analyze the empirical data. Z-scores and a sign test were used (Bortz & Doring, 2002). Additionally, effect sizes were calculated (Cohen, 1988).

3. 2. 4. Results

Figure 7: Flow diagram: IPT-TAU (TRS, NTRS) study

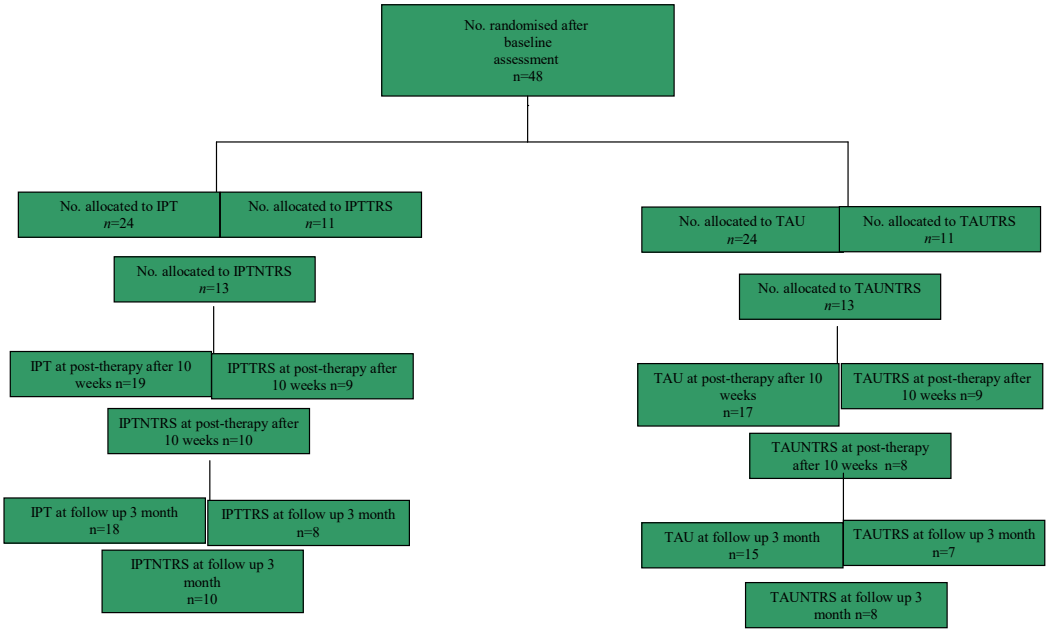


Fig. 7 Consort diagram: Flow diagram for IPTTRS, IPTNTRS and TAUTRS, TAUNTRS group.

Figure 7 shows the flow-diagram of the study. There was a significant difference regarding medication (chlorpromazine equivalents) between the groups TRS and NTRS. Table 3 shows the characteristics of the patients. Eleven patients of the IPT group (45.8%) belonged to TRS, while 13 (54.2%) belonged to NTRS. Eleven patients of the TAU group belonged to TRS (45.8%), while 13 with schizophrenia of the TAU group (54.2%) belonged to NTRS. Six patients of the group TRS (27%) take only clozapine. Seven patients (14.6%) (chisquare = 2.90; p = .08) of the group TRS and eight patients (16.7%) (chi-square = 3.84; p = .05) of the group NTRS dropped out. The reason for dropping out was low motivation (attendance rate<50%) to follow this project or relapse. Individuals with schizophrenia who relapsed were treated by psychiatrists of the adult psychiatric department and persons with schizophrenia, who showed low motivation, continued their psychiatric treatment, especially focusing on raising low motivation. Baseline analysis revealed significant differences between the comparison groups TRS and NTRS in the following variables: AVMT10 (verbal memory) $t(43) = 2.0$, $p = .04$, Aoveralqual (overall quality of life – Quality of life) $t(43) = 2.5$, $p = .01$, Apsychealth (psychological health – Quality of life) $t(43) = 2.3$, $p = .02$ and Asocrelat (social relationships – Quality of life) $t(43) = 2.2$, $p = .03$.

Table 3: Characteristics of the patients (IPT-TAU, TRS-NTRS

	IPT (24)		TAU (24)		t/Chi.Sq	*p*
	TRS (11)	NTRS (13)	TRS (11)	NTRS (13)		
	TRS (22)		NTRS (26)			
	M(SD)		M(SD)			
Age	31.3 (7.2)		33.8 (6.7)		1.2	0.22
	32.86(6.62)		32.26(7.42)		0.29	0.77
IQ (WAIS)	89.9 (9.4)		89.7 (7.7)		0.0	0.92
	88.18(7.89)		91.07(8.95)		1.17	0.24
Duration of illness (years)	5.4 (1.3)		5.9 (1.1)		1.4	0.16
	6.0(1.11)		5.38(1.29)		1.74	0.08
Medication (chlorpromazine equivalents)	542.1 (391.1)		512.1 (355.0)		0.28	0.78
	666.13(465.23)		409.42(209.48)		2.53	0.01
Gender (% male)	67		67		0.0	1.0
	59.1		73.1		1.04	0.30

Continued Table 3

Antipsychotics (% Atypical)	83.3 100.0	83.3 96.2	0.0 0.86	1.0 0.35

Note: M: Mean, SD: Standard Deviation, t: test, ChiSq: chi-square test.

Table 4: General linear model (GLM) for repeated measures (IPT-TAU, TRS-NTRS)

		T1	T2	T3	GLM T1-T2		GLM T1-T2-T3	
		M(SD)	M(SD)	M(SD)	F	*p*	F	*p*
Proximal outcome								
Neurocognition								
Vigilance (Continuous Performance Test)								
CPT Omission	TRS	3.66(6.59)	3.06(5.88)	1.40(2.38)				
	NTRS	2.83(3.41)	1.55(2.52)	1.33(4.0)	0.21	0.64	0.18	0.66
Working memory (Letter Number Span)								
LNS	TRS	13.93(4. 94)	16.13(4.53)	13.53(4.64)				
	NTRS	12. 50(3. 71)	15.77(4.13)	16.66(3.42)	0.09	0.76	0.37	0.54
Verbal memory (Verbal memory Test)								
VMT10	TRS	9.40(2.97)	10.13(2.92)	10.0(4.69)				
	NTRS	10.83(2.64)	12.50(2.09)	11.50(3.12)	**7.35**	**0.01**	3.81	0.06
Social Cognition								
Social Cognition (Social Perception Scale)								
SPST								
Stimulus	TRS	16.60(7.04)	26.80(14.46)	29.93(21.06)				
	NTRS	18.88(7.72)	33.00(17.14)	33.05(17.24)	0. 63	0.43	2.35	0.13
SPST								
Interpretation	TRS	6.20(1.65)	8.46(2.47)	8.33(3.69)				
	NTRS	6.02(1.02)	8.38 (2.52)	9.16(3.46)	1.13	0.29	0.13	0.71

Continued Table 4

SPST								
Title	TRS	3.53(2.77)	8.13(4.35)	7.06(4.38)				
	NTRS	4.0(1.45)	7.44(4.54)	7.77(4.31)	0.34	0.56	0.006	0.94
Distal outcome								
Symptoms								
Positive symptoms								
Panss								
Positive symptoms	TRS	28. 13(6.17)	25.0(4.69)	22.86(5.11)				
	NTRS	25.33(7.14)	20.22(5.62)	16.83(4.88)	3.61	0.06	**6.55**	**0.01**
Symptoms								
Negative symptoms								
Panss								
Negative symptoms	TRS	34.0(6.16)	30.33(5.76)	28.60(5.42)				
	NTRS	31.0(6.07)	26.05(4.30)	24.27(4.23)	1.93	0.17	**7.37**	**0.01**
Symptoms								
General Psychopathology								
Panss								
General Psychopathology	TRS	62.06(11.09)	55.13(8.53)	55.06(12.83)				
	NTRS	55.06(12.83)	45.83(10.75)	41.55(9.84)	2.72	0.10	**7.05**	**0.01**
Symptoms								
Insight								
Panss insight	TRS	4.53(0.99)	3.66(1.17)	3.33(1.04)				
	NTRS	4.05(1.39)	3.27(1.17)	2.83(0.98)	1. 13	0.29	1.95	0.17

Continued Table 4

Functional recovery						
GAF	TRS	34.0(12.13)	37.93(9.88)	43.80(8.18)		
	NTRS	41.44(13.67)	49.11(14.42)	61.50(13.19)	**5.49 0.02**	**10.33 0.03**
Functional recovery						
Quality of life						
Overal quality of life	TRS	11.80(4.37)	14. 26(3.28)	12.86(4.42)		
	NTRS	15.11(2.39)	15.22(2.66)	16.22(2.73)	**4.78 0.03**	**6.31 0.01**
Functional recovery						
Quality of life						
Psychological health	TRS	12.42(3.20)	12.70(2.98)	12.99(3.16)		
	NTRS	14.22(2.38)	14.48(1.86)	14.13(1.83)	3.06 0.08	**6.85 0.01**
Functional recovery						
Quality of life						
Social relationships	TRS	12.28(2.89)	13.44(3.02)	12.69(3.45)		
	NTRS	13.86(2.64)	13.77(3.09)	14.53(1.78)	1.21 0.27	2.27 0.14

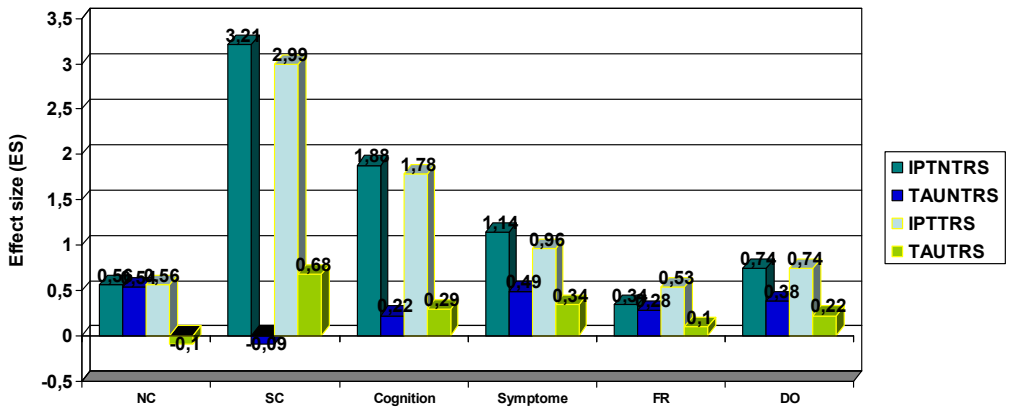
Note: **Bonferroni correction (Type I error): α=.05**

Table 5: Sign test: TRS (IPT, TAU) and NTRS (IPT, TAU)

Domain-Group	Median (T1)	Median (T2)	Median(T3)	positive differences	negative differences	ties	*p* p<.05	*z*
Proximal outcome Neurocognition								
IPTTRS	7. 99	9. 83		9	0	0	.004	2.65
IPTNTRS	7. 54	9.43		10	0	0	.002	2.87
IPTNTRS	7. 54		9. 69	10	0	0	.002	2.87
Social Cognition								
IPTTRS	9. 0	19. 33		9	0	0	.004	2.65
IPTTRS	9. 0		19. 33	9	0	0	.004	2.65
IPTNTRS	9. 0	23. 00		10	0	0	.002	2.87
IPTNTRS	9.0		23. 00	10	0	0	.002	2.87
Distal outcome Symptoms								
IPTTRS	41.66		32. 0	0	9	0	.004	2.65
IPTNTRS	37. 0		27. 66	0	10	0	002	2.87
TAUNTRS	42.33		34. 66	0	6	2	.03	1.88
Functional Recovery								
IPTNTRS	18.13	20.25		9	1	0	.02	2.05
IPTNTRS	18.13		22.46	10	0	0	.002	2.87
Distal outcome (Symptoms & Functional Recovery)								
IPTNTRS	25.08	22.26		0	10	0	002	2.87

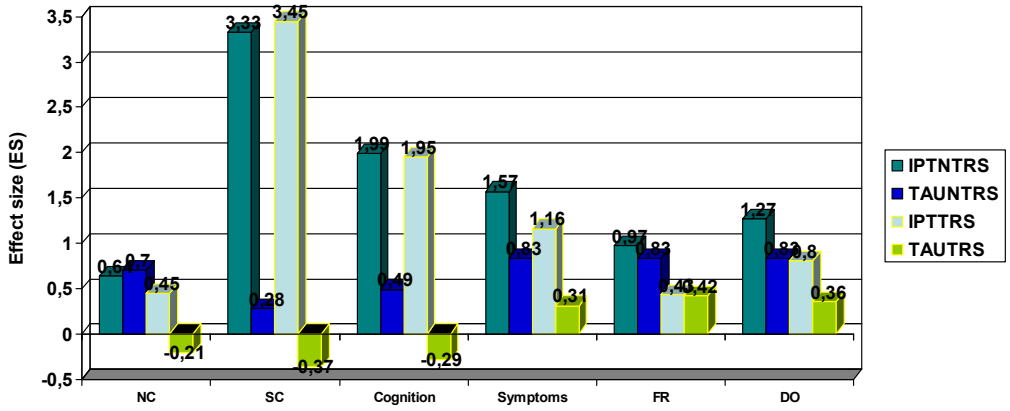
Note: IPTTRS: Integrated Psychological Therapy treatment resistant schizophrenia; IPTNTRS: Integrated Psychological Therapy non treatment resistant schizophrenia; TAUNTRS: Treatment as Usual non treatment resistant schizophrenia; positive differences: improvement; negative differences: decrease; ties: no change.

Figure 8: Effect sizes within groups T1-T2



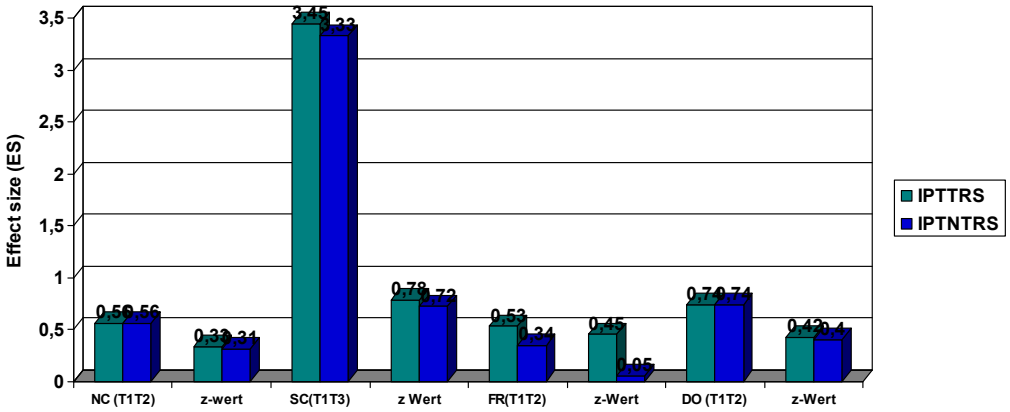
Note: NC: Neurocognition, SC: Social Cognition, FR: Functional Recovery, DO: Distal outcome

Figure 9: Effect sizes within groups T1-T3



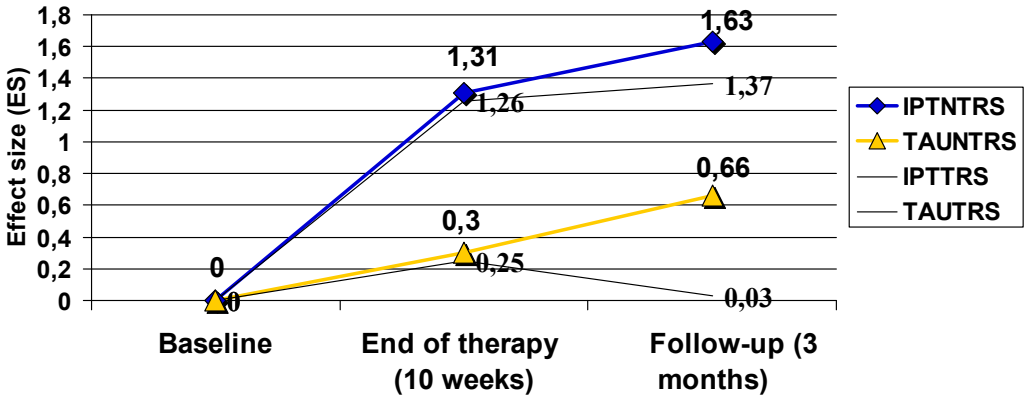
Note: NC: Neurocognition, SC: Social Cognition, FR: Functional Recovery, DO: Distal outcome

Figure 10: Effect sizes and z-scores



Note: NC: Neurocognition, SC: Social Cognition, FR: Functional Recovery, DO: Distal outcome

Figure 11: Total Therapy Effect T1-T3



3. 2. 5. Discussion

This is the first RCT study in Greece and internationally regarding the hypothesis, when IPT is more and when less effective in persons with schizophrenia. In other words, the study focuses on the interaction between IPT and TAU and NTRS and TRS. Nontreatment schizophrenia group showed better results in verbal memory; positive, negative symptoms and general psychopathology; functional outcome and the quality of life.

Effect sizes show superiority of NTRS in comparison to TRS in composite scores of cognition (proximal outcome), distal outcome and the total therapy outcome. The z-scores showed superiority of IPTTRS in neurocognition, social cognition, functional recovery and distal outcome in comparison to IPTNTRS, TAUTRS, and TAUNTRS.

The sign test showed a significant improvement in IPTTRS in neurocognition, social cognition, and symptoms, a significant improvement in IPTNTRS in neurocognition, social cognition, symptoms, functional recovery and distal outcome. Finally, the sign test showed a significant improvement in TAUNTRS in symptoms.

In other words, the main hypothesis of this RCT study is answered in the context of a first RCT study internationally regarding the question, when IPT is more effective. IPT is more effective under the circumstances of an NTRS. The IPTTRS, on the other side, also showed some improvements, which are maintained in the follow-up. The low drop out of patients in TRS group highlights that the participation in a structured evidenced based psychotherapeutic program increases the possibility of remaining in psychotherapy.

The low drop out in the IPT Group (TRS and NTRS) shows a positive acceptance of the treatment and of the ability of IPT to raise motivation and activate the resources of the patients, especially those with TRS.

The number of studies with patients with TRS and psychotherapeutic intervention or rehabilitation and cognitive remediation is small (Seppälä, Molins, Miettunen, Hirvonen, & Corripio, 2016). Thus, this study probably offers the empirical data for health service research, and for public and private mental health in psychiatry and clinical psychology, regarding the implementation of one of the most evaluated rehabilitation programs for people with schizophrenia in TRS and NTRS.

This result is in accordance with studies regarding IPT (Rakitzi et al., 2016; Roder et al., 2011)—a recovery-oriented therapy for persons with schizophrenia. Limitations and future implications are discussed.

The RCT of larger sample sizes is necessary to evaluate further the impact of IPT on TRS in comparison to NTRS. Further RCTs are necessary to evaluate the impact of pharmacotherapy, cognitive behavioral therapy in combination with rehabilitation programs such as IPT on individuals with schizophrenia and TRS.

3. 3. The recovery process for individuals with schizophrenia in the context of evidence-based Psychotherapy and rehabilitation. A systematic review.

Paper 5: Rakitzi, S., Georgila, P., & Becker-Woitag, P. (2020). The recovery process for individuals with schizophrenia in the context of evidence-based Psychotherapy and rehabilitation. A systematic review. *European Psychologist,* doi/pdf/10.1027/1016-9040/a000400

3. 3. 1. Abstract

This systematic review aimed to evaluate the efficacy of Cognitive Behavioral Therapy (CBT), of Meta Cognitive Therapy (MCT), of Metacognitive Training (MCTR), of Metacognitive Reflection and Insight Therapy (MERIT) and of various rehabilitations and recovery programs. The methodological quality of the included studies was evaluated by two independent raters, which are the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies and the fidelity criteria. The study included 41 RCTs and 12 case studies with n = 3,059 persons with schizophrenia. All the above interventions are efficacious for individuals with schizophrenia. It is recommended to combine the above evidence based psychotherapeutic interventions. Limitations of this systematic review are discussed toward the end of the essay. Some important factors have to be discussed.

The importance of this study (Rakitzi et al., 2020) is the presentation of the evidence based psychotherapeutic interventions only for individuals with schizophrenia regarding the recovery process. The hypotheses are answered through a systematic review, which is published online in European psychologist (Rakitzi et al., 2020).

3. 3. 2. Introduction

This systematic review aims to provide a comprehensive review about the efficacy of CBT, MCT, MCTR, MERIT, Rehabilitation and Recovery programs, which promote objective and subjective recovery in individuals with schizophrenia.

The systematic review answers the following questions regarding the objective and subjective recovery:

1. Is CBT efficacious for individuals with schizophrenia?
2. Is MCT, MCTR, and MERIT efficacious for persons with schizophrenia?
3. Are rehabilitation and recovery programs efficacious for persons with schizophrenia?

3. 3. 3. Material and Methods

This systematic review was conducted according to PRIMA guidelines (Liberatti et al., 2009). Included RCT and case studies were independently evaluated by the two researchers regarding the Effective Public Health Practice Project (EPHPP) quality assessment tool (Thomas, Ciliska, & Micucci, 2004) and regarding the treatment fidelity, according to the Treatment Fidelity Workshop of the National Institutes of Health Behavior Change Consortium (BBC) (Bellg et al., 2004).

3. 3. 4. Results

Figure 12: Flow diagram of the systematic review recovery

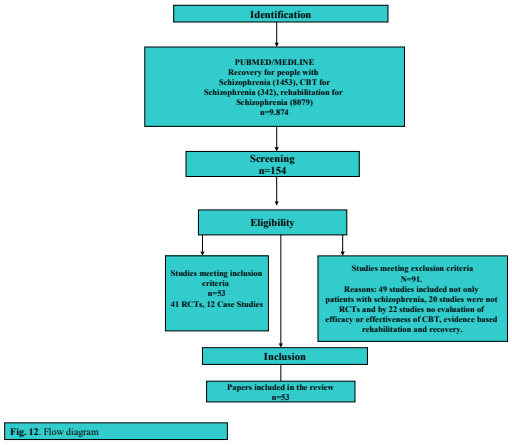


Fig. 12. Flow diagram

Forty one RCTs and 12 case studies with n=3059 persons with schizophrenia were included. The majority of patients were outpatients, men, and between 20–58 years of age.

Table 6: Characteristics of the RCT studies

Table 7: Characteristics of the Case Studies

The RCTs and the case studies improved cognition, symptoms, functional outcome, quality of life, self esteem, insight, comorbid disorders and meta cognitive deficits.

Table 6: Characteristics of the RCT studies

Study country quality	study design	n	intervention group	control group	follow up	outcome	
1.Guo et al. 2017 China strong	RCT	n=220 n=110 CBT n=110 TAU	CBT 8 sessions	TAU	yes	CBT better symptoms, insight, functioning	
2. Echeburua et al., 2011 Spain	RCT	n=44 n=23 CBT n=21 Control	CBT and drug therapy 20 sessions	drug therapy	yes	CBT decrease pathological gambling	strong
3. Gottlieb et al., 2017 USA strong	RCT	n=37 n=19 (CBT) n=18 (TAU)	web-based CBT 10 modules	TAU	yes	CBT better in social functioning and knowledge about CBT	
4. Naeem et al., 2015 Canada	RCT	n=116 n=59 CBT n=57 TAU	CBT (6-10 sessions)	TAU	no	CBT better in symptoms	strong
5. Tsiachristas et al., 2018 UK	RCT	n=43 n=19 CBT n=24 TAU	CBT (8 sessions)	TAU	yes	CBT improve better insomnia	moderate

Continued Table 6

6. Velligan et al., 2015 USA	RCT	n=166 n=41 CAT n=43 CBT n=40 CBT+CAT n=37 TAU	CBT, CAT, CBT & CAT (38 sessions)	TAU	yes	CBT did not improve outcomes. CBT and CAT did not improve outcomes more than CAT alone	strong
7. Klingberg et al., 2011 Germany	RCT	n=198 n=99 CBT n=99 CR	CBT (20 sessions)	CR (5 sessions)	Yes	Both groups improved in negative symptoms	strong
8. Poletti et., 2010 Italy	RCT	n=100 n=58 CRT n=42 control	CR (12 weeks)	control	Yes	CRT improved better in cognitive functions and daily functioning	strong
9. Bio & Gattaz, 2011 Brazil	RCT	n=112 n=57 VR n=52 control	VR (6 months)	control	No	VR improved cognitive functions, negative symptoms and quality of life	strong
10. Veltro et al., 2011 Italy	RCT	n=24 n=12 (CER) n=12 (PST)	CER (12 months)	PST (12 months)	No	Both trainings are effective in psychopathology and social functioning. PST improved Neurocognition and CER improved social cognition	strong

Continued Table 6

11. Bowie et al., 2012 USA	RCT n=114 n=38 (CR) n=38 (FST) n=38 (CR + FST)	CR (24 weeks) FST (24 weeks)	CR + FST (24 weeks)	Yes	Cognitive remediation improved neurocognition. Functional competence was improved, when skills training and cognitive remediation were improved.	strong
12. Gharaeipour & Scott, 2012 Iran-USA	RCT n=42 n=21 (CRT) n=21 (control)	CR (40 hours)	control	No	CR showed improvements in neurocognition, in depression and in negative Symptoms	strong
13. Man et al., 2012 Hong Kong	RCT n=80 n=27 (CCR) n=23 (TCR) n=30 (Control)	CCR (12 sessions) TCR (12 sessions)	control	Yes	CCR and TCR improved better neurocognition and vocational outcomes	strong
14. Garrido et al., 2013 Spain	RCT n=67 n=38 (CR) n=29 (control)	CR (48 sessions)	control	No	CR improved in neurocognition, quality of life and self esteem.	strong

Continued Table 6

15. Byrne et al., 2013 Australia China	RCT	n=31 n=14 (CRT) n=17 (TAU)	CR (12. 78 sessions)	TAU	No	CR improved attention, positive and negative symptoms	strong
16. Tao et al., 2015 China	RCT	n=86 n=44 (CRT) n=42 (Control)	CR (12 weeks)	drug therapy	Yes	CR reduced the relapse, improved the employment rate and decreased the discharged time	strong
17. Pena et al., 2016 Spain	RCT	n=107 n=52 (REHACOP) n=52 (control)	REHACOP (39 sessions)	occupational therapy	No	REHACOP improved neurocognition, social cognition, negative symptoms and functional disability	strong
18. Ojeda et al., 2012 Spain	RCT	n=93 n=47 (REHACOP) n=46 (control)	Rehacop (36 sessions)	Occupational therapy	No	REHACOP improved in cognition, in positive symptoms, in functioning and in insight.	strong
19. Wang et al., 2013 China	RCT	n=140	psychosocial rehabilitation (6 months)	drug therapy	Yes	PR decreased relapse and improved symptoms and social functioning	strong

Continued Table 6

20. Iwata et al., 2017 Japan	RCT n=60 n=29 (CR) n=31 (TAU)	CR (12 weeks)	TAU	No	CR improved neurocognition, interpersonal relationships and work skills	strong
21. Sanchez et al., 2014 Spain	RCT n=92 n=38 (REHACOP) n=54 (control group)	REHACOP 36 sessions	TAU	No	REHACOP improved in neurocognition, negative symptoms and functioning	strong
22. Gomar et al., 2015 Spain	RCT n=130 n=43 (CR) n=44 (CC) n=43 (TAU)	CR (48-sessions) CC	TAU	No	Computerized CR is not effective in schizophrenia	strong
23. Gharaeipour & Scott, 2012 Iran & USA	RCT n=42 n=21 (CR) n=21 (TAU)	CR (40 hours)	TAU	No	CR improved cognition and and decreased symptoms	strong
24. Subramaniam et al., 2014 USA	RCT n=30 n=15 CR n=13 CG N=12 TAU	CR (80 hours) CG (80 hours)	TAU	Yes	CR improved working memory and increased brain activity	strong

Continued Table 6

25. Kurtz et al., 2015 USA	RCT n=64 n=32 CR+SST n=32 control + SST	CR (50 hours) + control	control	No	CR improved in neurocognition and empathy	strong
26. Deste et al., 2014 Italy	RCT n=54 n=15 (IPT) n=22 (CR) N=17 (TAU)	IPT(CT) CR	TAU	Yes	The effectiveness of CR persists after one year	strong
27. Thomas et al., 2018 USA	RCT n=46 n=24 (TCR) n=22 (TAU)	TCR 40 hours	TAU	No	TCR improved verbal learning and auditory perception and reduced the auditory hallucinations	moderate
28. Choi et al., 2018 Korea	RCT n=38 n=19 CR + PR n=19 PR n=19 TAU	CR + PR (20-24 sessions)	TAU	No	CR improved in cognition (logical memory and executive functions)	strong

Continued Table 6

29. Rocha & Quieros, 2013 Portugal	RCT n=35 n=19 MSCT n=16 TAU	MSCT (18 sessions)	TAU	No	MSCT improved in social cognition, in social functioning and reduced the jumping to conclusions	strong
30. Bechi et al., 2013 Italy	RCT n=30 n=19 TOMI n=11 TAU	TOMI (18 sessions)	TAU	No	TOMI improved Theory of Mind abilities	strong
31. Souto et al., 2018 Spain	RCT n=61 n=30 ET n=31	ET (12 sessions ET)	TAU	No	ET improved emotion recognition and other TOM variables	strong
32. Sevos et al., 2018 France	RCT n=31 n=16 (Cinemotion) n=15 Control	Cinemotion (10 sessions)	TAU	No	Cinemotion improved recognition and expression of facial emotions	strong

Continued Table 6

33. Palumbo et al., 2017 Italy	RCT n=10 pilot n=5 (Social) n=5 (SSANIT)	Social (40 sessions)	SSANIT 40 sessions	No	Social improved social cognition and avolition	strong
34. Gil-Sanz et al., 2016 Spain-USA	RCT n=44 n=20(PECS-SCT) n=24 control	PECS-SCT (28 sessions)	Control	No	PECS improved theory of mind and emotion recognition	strong
35. Taylor et al., 2016 UK	RCT n=36 n=21 SCIT n=15 TAU	SCIT (16 sessions)	TAU	No	SCIT improved facial affect recognition. SCIT is effective in a forensic ward setting	strong
36. Gaudelus et al., 2016 France	RCT n=40 n=21 GAIA n=19 RECOS	GAIA (30 sessions)	RECOS (30 sessions)	No	GAIA improved facial emotion recognition, symptoms and social functioning	strong
37. Mueller et al., 2015 Switzerland	RCT n=156 n=81 INT n=75 TAU	INT (30 sessions)	TAU	Yes	INT improved neurocognition, social cognition and functioning	strong

Continued Table 6

38. Mueller et al., 2017 Switzerland	RCT n=61 n=28 INT n=33 TAU	INT (30 sessions)	TAU	Yes	INT improved in attention and in functioning.	strong
39. Rakitzi et al., 2016 Greece	RCT n=48 n=24 (IPT) n=24 (TAU)	IPT (20 sessions)	TAU	Yes	IPT improved in working memory, in social cognition, in symptoms and in insight	strong
40. Lin et al., 2013 Taiwan	RCT n=97	IMR	TAU	Yes	IMR improved illness management knowledge, attitudes toward medication insight and negative symptoms	strong
41. Vohs et al., 2018 USA	RCT n=20 n=10 (MERIT) n=10 (TAU)	MERIT (24 sessions)	TAU	No	MERIT improved Insight	strong

Table 7: Characteristics of the Case Studies

Study Country	Study design	n	Intervention	Outcome
1. Mankiewicz & Turner 2014 UK	Case study	1	Cognitive behavioural therapy (CBT) 16 sessions	CBT improved delusional appraisals of auditory hallucinations and comorbid anxiety
2. Grant et al., 2014 USA	Case study	1	(CBT) 70 sessions	CBT improved psychosocial functioning and positive neurocognitive performance, reduced symptoms and avolition and contributed to an avoidance of hospitalization
3. Izuhara et al., 2018 Japan	Case study	1	CBT-insomnia 8 sessions	CBT improved sleep. This decreased hallucinations and improved concentration
4. Inchausti et al., 2017 Spain	Case study	1	Metacognition oriented social skills training (MOSST) 16 sessions	The social acceptability of the patients behaviour has been improved and its disruptive behaviour has been decreased.

Continued Table 7

5. De Jong et al., 2016 Netherlands	Case study	1	Meta cognitive therapy 12 sessions	The therapy improved the metacognitive capacity
6. Balzan & Galletly 2015 Australia	Case study	1	Meta cognitive therapy 4 sessions	The therapy improved clinical insight and decreased delusions.
7. Levaux et al., 2012 Belgium	Case study	1	Goal Management Training 16 sessions	GML improved executive functions and self-esteem
8. Quee et al., 2012 Netherlands	Case study	2	Cognitive Adaptation Training (CAT) 8 months	CAT improved functional outcome
9. Peyroux & Franck, 2016 France	Case study	2	RC2S 14 sessions	RC2S improved social cognition and functioning
10. Leonhardt et al., 2016 USA	Case study	1	MERIT 72 sessions	MERIT improved metacognitive deficits

Continued Table 7

11. Leonhardt et al., 2018 USA	Case study	1	MERIT (in first episode psychosis)	MERIT improved metacognitive deficits
12. Hamm & Leonhardt et al., 2016 USA	Case study	1	Integrative recovery psychotherapy (IRP) (Interpersonal & MERIT) an ongoing psychotherapy	IRP improved metacognition

3. 3. 5. Discussion

In this systematic review, we provide a review regarding the efficacy of CBT, MCT, MCTR, MERIT, Rehabilitation, and Recovery Programs, which promote objective and subjective recovery in individuals with schizophrenia.

CBT showed improvement in symptoms and general psychopathology, cognition, functioning, insight, and comorbid disorders, such as sleep disorders and pathological gambling, which decrease the quality of life and increase psychotic symptoms (objective recovery).

Deficits in meta cognition have a negative impact on schizophrenia as well as on the individual's ability to take responsibility for its personal recovery process (Lysaker et al., 2018a). Meta cognitive approaches (MCT, MCTR, and MERIT) improve meta cognitive deficits enhancing awareness of cognitive processes, self-understanding and self management (Lysaker et al., 2018). MERIT enhances a kind of recovery, which is personally meaningful and self-directed (Lysaker et al., 2018). In other words, meta cognitive treatments are associated with the objective as well as with the subjective recovery.

MCT was effective regarding the improvement of metacognitive capacity and clinical insight and reduced positive symptoms (Balzan & Galletly, 2015; de Jong et al., 2016) (objective and subjective recovery).

MCTR decreased the disruptive social behavior in combination with social skills training (Inchausti et al., 2017) and improved social cognition as well as social functioning decreasing positive symptoms (jumping to conclusions) in combination with social cognition training (Rocha & Quieros, 2013) (objective and subjective recovery).

MERIT improved insight and metacognitive deficits (Hamm & Leonhardt, 2016; Leonhardt et al., 2016, 2018; Vohs et al., 2018) (objective and subjective recovery). The concept of ongoing Integrative psychotherapy of Hamm and Leonhardt (2016) needs further replication with the evaluation of the psychotherapy outcome in an evidence-based context.

CR, social-cognitive training, and integrative rehabilitation programs are efficacious for the improvement of cognition (neurocognition and social cognition), symptoms, and functioning (objective recovery).

Integrative programs are preferable due to better generalized effects (Bowie et al., 2012; Penades, Catalan, Pujol, Masana, Garcia-Rizo, & Bernardo, 2012; Roder et al., 2011) (objective recovery).

IMR showed better improvement in illness-management knowledge, attitudes towards medication, insight, and negative symptoms (Lin et al., 2013) (objective and subjective recovery).

It is recommended to combine CBT with CR (Klingberg et al., 2011; Penades et al., 2012). CBT and CR together better improve the negative symptoms (Klingberg et al., 2011).

Majority of the included studies have taken into consideration the fidelity criteria (Bellg et al., 2004). It is recommended to address the fidelity criteria in every study directly, which was not the case in all the studies.

A follow-up evaluation after post-treatment could provide more evidence regarding the enactment of treatment skills. Twenty four of the included RCTs did not include a follow-up evaluation (see Table 1), whereas three of the them did (Balzan & Galletly, 2015; Grant et al., 2014; Peyroyx & Franck, 2016).

The results of this systematic review are in line with other studies, which proved the efficacy of CBT, MCT, MCTR, MERIT, rehabilitation, and recovery programs, focusing on objective and subjective recovery (Burns et al., 2014; De Jong et al., 2018; Hofmann et al., 2012; Eichner & Berna, 2016; Lysaker et al., 2018; Lysaker et al., 2018a; Moritz et al., 2016; Roder et al., 2011; Mueller et al., 2013; Mueser et al., 2006; Wykes et al., 2011; Kurtz & Richardson, 2012; Kurtz et al., 2016).

More effective treatments for people with schizophrenia must be developed (Jääskeläinen et al., 2013).

There are some factors, which have to be probably considered by studies regarding the efficacy of CBT, MCT, MCTR, MERIT recovery, and rehabilitation and which can contribute to the improvement of recovery outcomes:

Are the therapists well trained and experienced?

Cognitive dysfunctions of the persons with schizophrenia contribute to the fact that these people need more time to learn and implement into their daily routine. Therefore, it could be wiser to offer long-term CBT and rehabilitation, as suggested by Grant et al. (2014), who offer 70 sessions. Additionally, it is recommended to offer long-term follow ups to evaluate this learning process.

Last, the combination of CBT, MCT, MCTR, MERIT, and rehabilitation programs could be probably a better and more effective strategy for long-term advantages for a chronic disease, such as schizophrenia. The recovery programs, such as the IMR, enhance the recovery process directly, whereas CBT, MCT, MCTR, MERIT and rehabilitation activate the recovery indirectly. Does being given the combined implementation of IMR with CBT, MCT, MCTR, MERIT, and rehabilitation in the long term more advantages to persons with schizophrenia? This combination could probably increase the efficacy of the interventions.

Our systematic review has its own limitations:

The focus of published studies is in the period 2010–2018.

A meta analysis will give better answers regarding the efficacy of CBT, MCT, MCTR, MERIT, rehabilitation programs, and recovery programs or the combination of all of them.

4. Discussion

IPT is one of the most evaluated group cognitive behavioral rehabilitation programs for individuals with schizophrenia. IPT was implemented for the first time in Greece following the paradigma of other countries.

IPT showed high significant effects in neurocognition (working memory), in social cognition (social perception), in psychopathology (negative symptoms, general symptoms) and in insight during therapy as well as during therapy and the follow up. No effects were found for positive symptoms and psychosocial functioning. A significant effect favoring TAU in quality of life was found at the follow-up. The calculation of effect sizes between IPT and TAU showed a large effect size after therapy favouring IPT (d=0.95), that could be maintained at follow-up (d=0.97).

Effect sizes within the groups concerning all the variables of the study were also calculated during therapy and during therapy and follow up. IPT showed superiority in all the domains. TAU was only superior to IPT in quality of life in the follow up. The total therapy effect size showed superiority of IPT in comparison to TAU during therapy and during therapy and the follow up.

The above results (Rakitzi et al., 2016) are in line with the Meta analyses regarding IPT (Mueller et al., 2013; Roder et al., 2011).

Further RCTs of adequate sample size, together with a longer follow-up plus active control conditions should also be included in the social part of IPT, in order to improve the benefit of evidence-based integrated intervention based on cognitive remediation in IPT procedure.

Rakitzi & Georgila, (2019), is the first RCT study in Greece and internationally regarding the hypothesis, when IPT is more and when less effective in persons with schizophrenia. In other words, the study focuses on the interaction between IPT and TAU and NTRS and TRS.

NTRS showed better results in verbal memory; positive, negative symptoms and general psychopathology; functional outcome and the quality of life. Effect sizes show superiority of NTRS in comparison to TRS in composite scores of cognition (proximal outcome), distal outcome and the total therapy outcome.

The z-scores showed superiority of IPTTRS in neurocognition, social cognition, functional recovery and distal outcome in comparison to IPTNTRS, TAUTRS, and TAUNTRS.

The sign test showed a significant improvement in IPTTRS in neurocognition, social cognition, and symptoms and a significant improvement in IPTNTRS in neurocognition, social cognition, symptoms, functional recovery and distal outcome. Finally, the sign test showed a significant improvement in TAUNTRS in symptoms.

IPT is more effective under the circumstances of an NTRS. The IPTTRS, on the other side, also showed some improvements, which are maintained in the follow-up.

Treatment resistant schizophrenia present a challenge as well as a complicated issue in research and in clinical praxis. The more effective treatments in the context of a multimodal therapy are available, the higher are the possibilities of enhancing the recovery process in people with schizophrenia. The Integrated Psychological Therapy can be an effective treatment for treatment resistant schizophrenia.

An RCT of larger sample sizes is necessary to evaluate further the impact of IPT on TRS in comparison to NTRS. Further RCTs are necessary to evaluate the impact of pharmacotherapy, cognitive behavioral therapy in combination with rehabilitation programs such as IPT on individuals with schizophrenia and TRS.

Rakitzi et al., (2020) present a review regarding the efficacy of CBT, MCT, MCTR, MERIT, Rehabilitation, and Recovery Programs, which promote objective and subjective recovery in individuals with schizophrenia. Fifty-three studies were included: 41 RCTs and 12 case studies. All the above interventions are efficacious regarding the improvement of cognition, symptoms, functioning, comorbid disorders and meta cognitive capacity and therefore enhance the objective and subjective recovery process.

There are some factors, which have to be probably considered in the future:

Does being given the combined implementation of IMR with CBT**,** MCT, MCTR, MERIT, and rehabilitation in the long term more advantages to persons with schizophrenia? This combination could probably increase the efficacy of the interventions.

Are the therapists well trained and experienced?

Cognitive dysfunctions of the persons with schizophrenia contribute to the fact that these people need more time to learn and implement into their daily routine. Therefore, it could be wiser to offer long-term CBT and rehabilitation, as suggested by Grant et al. (2014), who offer 70 sessions. Additionally, it is recommended to offer long-term follow ups to evaluate this learning process.

Last, the combination of CBT, MCT, MCTR, MERIT, and rehabilitation programs could be probably a better and more effective strategy for long-term advantages for a chronic disease, such as schizophrenia.

The recovery programs, such as the IMR, enhances the recovery process directly, whereas CBT, MCT, MCTR, MERIT and rehabilitation activate the recovery indirectly. Does being given the combined implementation of IMR with CBT**,** MCT, MCTR, MERIT, and rehabilitation in the long term more advantages to persons with schizophrenia? This combination could probably increase the efficacy of the interventions.

Taken together, the 3 published studies (Rakitzi et al., 2016; Rakitzi & Georgila, 2019, Rakitzi et al., 2020) give an insight of the importance of the implementation of evidence-based psychotherapy and rehabilitation by persons with schizophrenia. IPT was implemented for the first time in Greek population following the paradigma of other countries. The impact of IPT in NTRS and TRS was taken into consideration for the first time internationally. Finally, the systematic review give an insight regarding the variety of evidence-based interventions for people with schizophrenia.

4. 1. Strengths and limitations of the papers

After the initial publication of the Greek version of IPT in 2007 (Roder et al., 2007), this RCT (Rakitzi et al., 2016) supports evidence for the feasibility of IPT procedure in patients with schizophrenia in Greece. The relatively low dropout rate and satisfying feedback by patients suggest a positive acceptance of the treatment. IPT could be implemented for the first time in a context of a psychiatric department of a general hospital in Greece.

This study makes such context possible and attractive for further rehabilitation initiatives with IPT and further research regarding the efficacy of IPT.

Lastly, the implementation of IPT in a country, such as Greece, which is confronted with a social and economic crisis, present an advantage for the individuals with schizophrenia and their families.

Following limitations must be mentioned:

1. The sample size was small.

2. The follow-up phase of three months may have been too short to identify possible stable generalization effects.

3. TAU may have been limited in controlling unspecific group effects of IPT treatment, which could be identified through an active control condition. TAU is on the other side a first step of evaluating the efficacy of IPT.

4. Matrics Consensus Cognitive Battery (MCCB) could be a more appropriate instrument to evaluate the cognitive functions of the patients with schizophrenia. There is no greek translation for MCCB.

5. GAF has its own limitations. It may be nicht so sensitive for psychosocial changes (Roberstson et al., 2013; Startup et al., 2002). More measures for social functioning could be included.

6. The implementation of the cognitive part of the IPT was a disadvantage. In order to benefit from this integrative treatment and to have better results in functioning, it is recommended to implement all the 5 subprograms of IPT.

Rakitzi & Georgila (2019), present an RCT, in which the hypothesis, when IPT is more and when less effective in persons with schizophrenia, is given consideration for the first time in Greece and internationally. The low drop out in the IPT Group (TRS and NTRS) shows a positive acceptance of the treatment and of the ability of IPT to raise motivation and activate the resources of the patients, especially those with TRS.

It highlights also, that the participation in a structured evidenced based psychotherapeutic program increases the possibility of remaining in psychotherapy.

The number of studies with patients with TRS and psychotherapeutic intervention or rehabilitation and cognitive remediation is small (Seppälä et al., 2016). Thus, this study probably offers the empirical data regarding the implementation of IPT in TRS and NTRS (Rakitzi & Georgila, 2019).

Following limitations have to be considered:

1. The sample size was small.

2. The follow-up phase of 3 months is very short. Patients with schizophrenia learn in a long term. A better generalization effect should be discovered in a follow up phase after several months.

4. We have implemented only the cognitive part of the IPT. It is recommended to implement the whole IPT in order to improve the functional recovery process.

Rakitzi et al., (2020) present a systematic review of modern evidence based psychotherapies only for individuals with schizophrenia. It gives a critical perspective towards the psychotherapies, which enhance the recovery process and the reintegration into society.

Following limitations have to be mentioned:

The focus of published studies is in the period 2010–2018.

A meta analysis will give better answers regarding the efficacy of CBT, MCT, MCTR, MERIT, rehabilitation programs, and recovery programs or the combination of all of them.

4. 2. Implications for research

Further RCTs with large samples, which evaluate the efficacy of IPT in Greek patients with schizophrenia and in other countries as well as the efficacy of IPT in TRS in Greece and other countries are on demand. The comparison of IPT with an active control group in a Greek sample is an important research goal. The implementation of all the 5 subprograms of IPT will offer better results in functional recovery.

Patients with schizophrenia learn in a long term. Follow ups in a long term are more able to highlight this learning process in a long term of the individuals with schizophrenia. Further RCTs with large samples, in which the efficacy of the combination of recovery programs, rehabilitation programs, CBT and metacognitive therapies is evaluated, are on demand.

4. 3. Implications for the clinical praxis

IPT was implemented in many countries. A contact with the Berner group (Prof. V. Roder) is appropriate, in order to implement this program. Therapists should be trained in cognitive behavioral therapy and then to any other program, such as IPT. The first implementation of a program, which improves the recovery process of the individuals with schizophrenia, should be made under supervision.

Lastly, today we cannot blaim that efficacious and effective therapeutic programs for individuals with schizophrenia are not available to the scientific community. We have many alternatives. Mental health experts are often not motivated enough to work with individuals with schizophrenia. We are obliged to develop a therapeutic plan offering best circumstances, in order to improve the recovery process of persons with schizophrenia.

5. Summary

IPT is one of the most evaluated group cognitive behavioral rehabilitation programs for individuals with schizophrenia. IPT was implemented for the first time in Greece and showed encouraging results in line with other studies (Mueller et al., 2013; Roder et al., 2011). Further RCTs are on demand.

IPT is more effective under the circumstances of an NTRS. The IPTTRS, on the other side, also showed some improvements, which are maintained in the follow-up. Further RCTs also internationally are also on demand.

Recovery programs, rehabilitation programs, CBT and meta cognitive approaches enhance effectively the recovery process of persons with schizophrenia. The combination of them in RCTs present a challenge. A meta-analysis regarding the combination of the above evidence based treatments is also on demand.

Vulnerable people, such as persons with schizophrenia, should have priority for us in the context of a democratic society!

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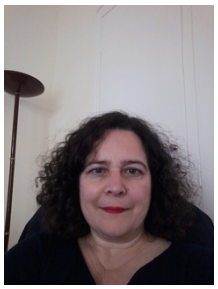
7. Curriculum Vitae



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EDUCATION AND TRAINING

1993/94-2000: Psychology Studies in GEORG-AUGUST-UNIVERSITY OF GÖTTINGEN in Deutschland. Dipl.-Psychologist (Diploma in Psychology).

2003/2004-2009: Diploma in Cognitive Behavioral Psychotherapy at the Institute of Behavioral Research and Therapy in Athens Greece.

2009-today: EuroPsy (EFPA): Europäisches Zertifikat in Psychologie

(from Bundesverband Deutscher Psychologen und Psychologinnen).

2010-today: Accrediation in Cognitive Behavioural Therapy from EABCT and the Hellenic Society for Behavioral Research and Therapy (www.eees.gr).

December 2017-today: (Cand.) Phd (Clinical Psychology) at the University Koblenz-Landau in Germany (Prof. A. Schröder)

WORK EXPERIENCE

10938/2001: Licence as Psychologist in Greece

2001-2002: Diplompsychologist (private employee) at the Hellenic CDC, department of the ministry of Health (working with HIV patients).

November 2003-today: Freelancher (Freiberuflerin Diplompsychologin), Private practice as Diplompsychologist and Cognitive Behavioral Psychotherapist.

2010-June 2017: Trainer in CBT at the Association for Cognitive Behavioural Studies http://cbt.edu.gr/erg/.

2017-today: Trainer in CBT in my own private practice

Memberships

Member of Bundesverband Deutscher Psychologen und Psychologinnen, (BDP), EABCT, ΕΕΕΣ (Hellenic Society for Behavioral Research and Therapy)

Awards

2005: Young Scientist award

Projects

2005-2017: Promotion of the Integrated Psychological Therapy (IPT) for patients with schizophrenia in Greece in cooperation with Prof Volker Roder and Dr. K. Efthimiou†, Managing director of the Institute of Behavioural Therapy and Research and Supervisor at the Association for Cognitive Behavioural Studies in Athens until 2017.

2009-2013: Implementation of IPT at the psychiatric department for adults at General Hospital Gennimatas in Athens

2009-2013: lectures about CBT for the psychiatrists in training at Gennimatas Hospital

2012-June 2017: Managing a trainings program to IPT at the Association for Cognitive Behavioural Studies in Athens

2010-2017: Trainer at the Association for Cognitive Behavioural Studies

July 2017-today: Managing a trainings program to IPT for psychologists and psychiatrists in my private practice

2013-today: Implementation of IPT in my private practice

Handling as a reviewer

Special Editor of the special issue “Clinical Counseling Psychology” of the Journal Acta Psychopathologica August 2017-December 2017

Special Editor of the special issue “Suicidal ideation and suicide” of the Journal Acta Psychopathologica, Februar 2018-

Invitation to review from: Psychiatry Research (2017), Open Psychology Journal (2016), European Psychologist (2019), British Journal of Clinical Psychology (2018), International journal of Psychiatry in clinical practice (2019), Psychotherapy Research (2019, 2020).

Publications (Books, chapters in books)

Rakitzi, S., & Georgila, P. (2018). The recovery process in the context of pharmacotherapy and CBT in patients with schizophrenia. In Avid Science (Eds), Schizophrenia. Avid Science.

Rakitzi, S., Georgila, P., & Efthimiou, K. (2017). Pharmacotherapy and Cognitive Behavioral Therapy for Patients with Schizophrenia. In Avid Science (Eds), Behavioral Therapy. Avid Science

Rakitzi, S., Georgila, P., Efthimiou, K. (Eds) (2016). Intervention by patients with schizophrenia. Athens: IBRT (Greek edition).

Rakitzi, S. & Georgila, P. (2016). Schizophrenia in teenagers. In Kalantzi, A., & Sofianopoulou, A. (Eds) (2016). CBT by children and teenagers (Greek edition)

Roder, V., Brenner, H. D., Kienzle, N., & Efthimiou, K. (2007) The Integrated Psychological Therapy. The Greek manual.

(Rakitzi, S., participation in the translation of the manual)

Publications (Journals)

Rakitzi, S., Georgila, P., & Becker-Woitag, A. P. (2020). The recovery process for individuals with schizophrenia in the context of evidence based psychotherapy and rehabilitation. A systematic review. *European Psychologist,* doi/pdf/10.1027/1016-9040/a000400.

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Rakitzi, S., Georgila, P., & Efthimiou, K. (2016). Insight and Rehabilitation of Patients with Schizophrenia. *Journal of Memory Disorders and Rehabilitation,*
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Efthimiou, K., Rakitzi, S., & Roder, V. (2009). Ένα γνωσιακό συμπεριφορικό ομαδικό θεραπευτικό πρόγραμμα για τη βελτίωση των γνωστικών και κοινωνικών δεξιοτήτων των ασθενών με σχιζοφρένεια. Ψυχιατρική (Psychiatriki), 20(3), 245-254. (A review about the Integrated Psychological Therapy in Greek).

Bandouna, Lysaker, P., & Rakitzi, S. (2015). New psychotherapeutic approaches to schizophrenia: Enhancing metacognitive capacities. *Γνωσιακή Συμπεριφοριστική Έρευνα και Θεραπεία,* 1(2), 95-103.

(A review about metacognitive therapy of schizophrenia patients, a new therapy approach from Prof Lysaker et al. Publication in the Hellenic Journal of Cognitive Behavioral Research and Therapy http://ibrt.gr/edu/node/533 (in Greek)

Vlassopoulou, A., & Rakitzi, S. (2016). Cognitive-behavioral psychotherapy in the treatment of traumatic stress, which is associated with child sexual abuse. *Γνωσιακή συμπεριφοριστική έρευνα και θεραπεία,* 2(1), 41-52.

(publication description: A review about CBT in PTSD after sexual abuse in the childhood in the Hellenic Journal of Cognitive Behavioral Research and Therapy http://ibrt.gr/edu/node/533) (in Greek).

Matsaka, A., & Rakitzi, S. (2017). The Good life model and its importance for the therapy of sexual offenders. A Review. *Γνωσιακή Συμπεριφοριστική Έρευνα και Θεραπεία,* 3(1), 49-57.

(Hellenic Journal of Cognitive Behavioral Research and Therapy) (in Greek) http://ibrt.gr/edu/node/533) (in Greek)

Kamboli, G., & Rakitzi, S. (2017). The therapeutic relationship and alliance and its importance in CBT. A review. *Γνωσιακή Συμπεριφοριστική Έρευνα και Θεραπεία,* 3(1), 5-17. (Hellenic Journal of Cognitive Behavioral Research and Therapy (in Greek).

Rakitzi, S., & Georgila, P. (2018). The evidence based interventions in the context of Cognitive behavioural Psychotherapy for patients with schizophrenia. *Γνωσιακή Συμπεριφοριστική Έρευνα και Θεραπεία,* 4(1), 5-13.

(publication description: A review about the evidenced based interventions in CBT by people with schizophrenia in the Hellenic Journal of Cognitive Behavioral Research and Therapy http://ibrt.gr/edu/node/533) (in Greek).

Conferences

Active participation on national (Greece) and international conferences as a speaker with oral presentations in symposia, workshops and with posters between 2002-2020:

National conferences (Greece): (Panhellenic Psychiatry conference, panhellenic conference for Cognitive Behavioral Therapy, panhellenic conference for Cognitive Behavioral Therapy in children and adolescents, Panhellenic conference for psychological research, Panhellenic conference of Clinical Psychology and Health Psychology, panhellenic conference for sexual abuse, Panhellenic Conference on Psychopharmacology, member of the organizing and scientific committee of a 2 day conference about interventions in schizophrenia in collaboration with the psychiatric department of General Hospital G. Gennimatas in Athens 2009).

International conferences: XIV International AIDS Conference (Barcelona, 2002), Verhaltenstherapiewoche in Freiburg Deutschland (2004), World Congress of World Federation for Mental Health, (2009 Athens), 2nd European Conference on Schizophrenia Research. From Research to Practice (Berlin, 2009), Internationales Schizophrenie-Symposium in Bern (2005, 2010), International Congress of the World Federation for Mental Health and the Hellenic Psychiatric Association: Living with schizophrenia (Athens, 2014), 5th International Congress on Psychiatry and the Neurosciences (Athens 2016). World Psychiatric Association: Thematic congress on intersectional collaboration: Psychological Trauma: global burden on mental and physical health (Athens, December 2020).

Issues of the presentations: Schizophrenia, sexual abuse, Integrated Psychological Therapy, Recovery for people with schizophrenia, Grief process of physicians and mental health experts, Cognitive Behavioral Therapy by patients with Cystic Fibrosis. A challenge during the pandemic of COVID-19.

8. Erklärung

Athen, 5/06/2020

Erklärung

Hiermit erkläre ich, dass ich die Dissertation selbst angefertigt hat und alle von mir benutzten Hilfsmittel in der Arbeit angegeben habe. Mein individueller Beitrag für die angereichten Zeitschriftenmanuskripte (Publikationsbasierte Promotion) kann folgendermaßen beschrieben werden: Koordination des gesamten Forschungsprojektes, Koordination und Supervision der Datenerhebung, Analyse und Interpretation der Daten, Schreiben und Úberarbeitung aller Manuskripte.

Ich habe die Dissertation oder Teile hiervon nicht als Prüfungsarbeit für eine stattliche oder andere wissenschaftliche Prüfung eingereicht. Ich habe nicht die gleiche oder eine andere Abhandlung bei einer anderen Hochschule als Dissertation angereicht.

Athen, 5/06/2020 Stavroula Rakitzi

9. Published papers

Psychiatry Research 242 (2016) 137–143

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Efficacy and feasibility of the Integrated Psychological Therapy for outpatients with schizophrenia in Greece: Final results of a RCT

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ABSTRACT

The goal of this study was to evaluate the efficacy and the feasibility of cognitive remediation group therapy in patients with schizophrenia in Greece. For this purpose, the cognitive part of the Integrated Psychological Therapy (IPT), focusing on neuro- and social cognition, was compared in a randomized controlled trial (RCT) with treatment as usual (TAU). 48 outpatients took part in the study. IPT groups received 20 biweekly 1-h-therapy sessions. A test-battery was assessed at baseline, after therapy, and at a 3-month follow-up. Regarding cognitive functioning, significant effects favouring IPT were found in working memory and social perception during therapy and at follow-up. No effects could be found in verbal memory and vigilance. Significant effects favoring IPT were found in negative symptoms, in insight and in general symptoms during therapy and at follow-up using the Positive and Negative Syndrome Scale (PANSS). No effects were evident in positive symptoms and in psychosocial functioning. Significant effects favoring TAU were found in the quality of life assessment at follow-up. The study supports evidence for the feasibility and efficacy of IPT in psychiatric care in Greece and it hopefully will initiate the broader use of evidenced-based treatments like IPT in Greek Psychiatry.

1. Introduction

Long-lasting functional deficits represent a challenge in the treatment of schizophrenia patients. 75–90% of all patients with schizophrenia suffer from cognitive deficits (Bell et al., 2013; Fett et al., 2013; Fioravanti et al., 2012; Green et al., 2012; Hovington et al., 2013; Roder and Mueller, 2008; Sachs, 2008; Ventura et al., 2013) A decade ago, the National Institute of Mental Health (NIMH) supported the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, to stimulate the development of pharmacological agents in treating cognitive deficits in schizophrenia, which are considered to be a core feature of the disorder. The following cognitive domains were initially recognized by MATRICS as being relevant for the treatment of schizophrenia: neurocognition: speed of processing, attention/vigilance, verbal and visual memory and learning, working memory, reasoning and problem solving; social cognition: emotion processing, social perception, Theory of Mind (ToM), social schema, attribution (Green et al., 2005; Nuechterlein et al., 2004; Nuechterlein and Green, 2006).

According to the NIMH-MATRICS Consensus Statement on Negative Symptoms, negative symptoms are common features for individuals suffering from schizophrenia. They are associated with poor function and quality of life and have been proposed as a separate domain since 1974. Some of the conclusions of the NIMH-MATRICS consensus Statements on negative symptoms are the following: 1. Negative symptoms constitute a distinct therapeutic indication area, 2. Negative symptoms and cognitive impairments represent separate domains 3. Negative symptoms have face validity as disease manifestations, and represent loss or diminution of normal functions (Buchanan, 2007; Kirkpatrik et al., 2006; Kirkpatrik, 2014; Velligan et al., 2014).

Pharmacological agents show only small effects in improving cognitive domains (Leucht et al., 2013; Tandon, 2011). Consequently, psychological therapy approaches become of major interest. Cognitive Remediation therapy (CRT) is the only approach intervening directly in the enhancement of some cognitive functions. Meta-analyses support efficacy of CRT in improving most of the MATRICS domains (Kurtz et al., 2001; Kurtz and Richardson,

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2012; McGurk et al., 2007; Wykes et al., 2011), but generally fail to improve a more distal outcome such as social functioning (McGurk et al., 2007). Integrated approaches combining CRT with other therapy topics seem to be far more successful in improving a more distal outcome (McGurk et al., 2007; Wykes et al., 2011). Cognitive rehabilitation in schizophrenia becomes an even more important treatment, since there is evidence that neurocognitive domains are linked to functional outcome and these connections are strongly mediated by social cognitive functions as well as negative symptoms (Green et al., 2012; Robertson et al., 2014; Schmidt et al., 2011; Strassnig et al., 2015; Ventura et al., 2014).

1.1. Integrated Psychological Therapy (IPT)

IPT is a comprehensive manualized group cognitive behavioural therapy approach, integrating interventions on neurocognition, social cognition and social functions in one therapy concept (Roder et al., 2008, 2010). Its conceptualization is based on the assumption that main deficits in cognitive domains have a pervasive effect on higher levels of behavioural organization such as social functioning. IPT is divided into 5 subprograms (SP) with increasing levels of complexity. It begins with intervention on neurocognition (SP1: Cognitive Differentiation) and social cognition (SP2: social perception), followed by intervention on communication skills (SP3: verbal communication), social skills (SP4) and interpersonal problem-solving skills (SP5). These 5 modular subprograms should be applied sequentially, but they have also been administered separately both in research and practice. A detailed description of the IPT concept is available as a manual (Roder et al., 2008), which has been translated into 13 languages (Efthimiou et al., 2009; Roder et al., 2007, 2010).

Over the past 30 years, research groups in 12 countries have evaluated integrated psychological therapy (IPT) in 37 independent studies, including 1632 schizophrenia patients. These studies on IPT were recently summarized and quantitatively reviewed in meta-analyses (Mueller et al., 2013; Roder et al., 2006, 2011). IPT revealed significant superior effects compared to Treatment as Usual (TAU), to active control groups in neurocognition, social cognition and functional outcome, as well as in the more distal outcome area of negative symptoms. All these favourable effects were maintained at follow-up. The positive results were very robust in respect to cited conditions and setting.

In this study, only the cognitive part of IPT (SP1, SP2, and the first two levels of SP3) was conducted. The SP3 aims to train basic communication skills: Hearing, Understanding and React. The first level of SP3 focuses on the precise repetition of sentences and the second level focuses on the repetition of the main meaning of a sentence (Roder et al., 2008, 2010). As a first implementation step, only the cognitive part of IPT was conducted: it is highly structured, easy to handle and needs only a limited time frame.

The aim of the study was to examine the following hypothesis: the IPT group shows better improvement in proximal outcome of neurocognitive and social cognitive functions. Moreover, IPT obtains superior effects in symptom reduction and in psychosocial functioning in comparison to the control group.

2. Methods

2.1. Study population

The outpatients were recruited from the outpatients department of the Psychiatric Department of the General Hospital "G. Gennimatas" in Athens. All patients, who participated in this project, were initially invited by the Director of the clinic for an interview, in which the research project was presented.

"G. Gennimatas" is one of the largest general hospitals in Greece. It consists from many departments, one of which is the psychiatric department. This psychiatric department contains an inpatient department, an outpatient department, liaison psychiatry and a hostel. Patients are offered psychiatric and psychological-psychotherapeutic treatment. In the past there was no initiative regarding the implementation of an evidenced based rehabilitation program for individuals with schizophrenia for improvement in neurocogntion and social cognition. That means that this study is the first implementation of an evidenced based rehabilitation program for improvement of neurocognition and social cognition by individuals with schizophrenia in this department and in a context of a general hospital in Greece.

The advantages and disadvantages of participating in this study were discussed in individual sessions with the patients and their families, separately. The patients have given informed consent to participate in the project. The patients were not paid for participation. It is common in the Greek mental health system care to include families in the therapy of individuals with schizophrenia, when the inter-family relationships are positive. The majority of these patients live with their families these last years of social and economic crisis.

Finally, the study protocol was approved by the Scientific Committee of the General Hospital "G. Gennimatas". A total of 48 outpatients took part in this study. The following inclusion criteria were used: Diagnosis of schizophrenia according to DSM-IV (American Psychiatric Association, 2004), IQ > 80, patients were between 20 and 50 years, the duration of the disease was more than two years, no excessive substance abuse, no brain disease, and no relapse 2 months before the study entry.

Changes in medications were allowed before the study intake, when necessary. The medication was controlled during the whole therapy at monthly sessions with the psychiatrists of the clinic. The medication did not change at all during the project.

The patients of this study had no experience regarding the participation in individual cognitive behavioural therapy or in an evidenced based rehabilitation program for the improvement of neurocognition, social cognition and symptoms.

2.2. Study design

This study summarized a randomized controlled trial (RCT). After a baseline assessment (T1), a randomization procedure took place: Patients were allocated the IPT group as experimental group and treatment as usual (TAU) as the control group using a random drawing of lots by an independent person. The second assessment was carried out after the 10 week intervention. The third and final assessment was carried out at a follow-up of three months after the end of therapy.

TAU was chosen for the control group because there were no additional staff-therapists for another control condition. This study is the first RCT study for the efficacy of IPT in Greece. TAU is recommended as a necessary first step in evaluating the efficacy of IPT.

2.3. Therapists

Two therapists led all the IPT groups: A Psychologist was the main therapist and a Psychiatrist was the co-therapist. Both are experienced psychotherapists and well educated in IPT procedure. One blinded rater with an MD degree, not participating in the study, conducted the assessments.

2.4. Intervention

The experimental group represents a cognitive remediation approach in a group therapy setting following the cognitive part of

IPT. This consisted completion of the first two subprograms of "Cognitive Differentiation" and "social Perception", along with the first two levels of the third subprogram "Verbal Communication". IPT groups received 20 biweekly therapy sessions over 10 weeks, in addition to TAU. Each therapy session lasted 60 min. The duration and frequency of 20 bi-weekly therapy session was chosen in accordance with the guidelines of the authors recommendation for the implementation of the cognitive part of IPT (Roder et al., 2008, 2010, 2011).

TAU is defined as standard medication, case management and individual supportive therapy by a psychiatrist or psychologist. Supportive therapy included non-specific intervention, which helped the outpatients to cope with problems in daily routine. It did not contain specific cognitive behavioural therapy techniques or goals referring to work therapy. TAU was used as a control condition to be compared with the experimental group. The TAU group received the same therapy as IPT regarding the intensity of the therapy. Our 2 comparison groups are in the range of the intensity of treatment of the studies summarized in the meta-analysis on IPT of Roder et al. (2006, 2011). Each of the groups consisted of 8 participants. 3 IPT and 3 TAU groups took part. An attendance rate of less than 50% was defined as drop out and was excluded from the analysis.

2.5. Measures

2.5.1. Cognition (proximal outcome)

The following standardized assessments of cognitive variables addressing proximal outcome were used in the study. The neurocognitive domain of vigilance/attention was evaluated with the Continuous Performance Test (CPT), which measures selective attention, vigilance or sustained attention and impulsive behaviour (Mass, 2002). Working memory was evaluated with the Letter Number Span (LNS) (Gold et al., 1997; Nuechterlein and Green, 2006) using the Greek translation (Rakitzi, 2007a). The Greek verbal memory Test (VMT) was used to assess verbal memory (Kosmidou, 2002). Finally, the social cognitive domain of social perception was assessed with a Greek translation of the Social Perception Scale (SPS).

The SP2 "social perception" of the IPT improves the ability of the patients to perceive and interpret social situations. The Social Perception Scale was developed to measure social perception, one of the components of social cognition, after the implementation of SP2. The SPS assesses the three main aspects of Social Perception Program of IPT: stimuli identification, interpretation of images, and title assignment. The SPS is an instrument to support the therapists decision, whether the patients are ready for the next subprogram or not. The correlation between pre-test and post-test measurements is high (.96–1.00) (Garcia et al., 2003; Rakitzi, 2007b; Ruiz et al., 2005).

2.5.2. Psychopathology (distal outcome)

Positive, negative and general symptoms were assessed using the Greek version of the Positive and Negative Syndrome Scale PANSS (Kay et al., 1987; Lykouras et al., 2005). A well-experienced and blinded rater (M. D. degree) conducted the PANSS interview.

2.5.3. Functional outcome (distal outcome)

Quality of life was assessed using the Greek version of the World Health Organization Quality of Life WHOQOL (Ginieri-Coccosis et al., 2003, 2012). Psychosocial functioning was assessed using the Global Assessment and Functioning scale GAF (American Psychiatric Association, 2004). GAF and PANSS were both conducted by the same blinder rater.

2.5.4. Data analysis

The SPSS Version 21 has been used for statistical analysis. The General linear model for repeated measurements (GLM) and *t*-test were chosen to treat analysis of the empirical data (Bortz and Döring, 2002). Additionally, effect sizes were calculated using the difference between the mean scores of the comparison groups divided by the pooled standard deviation (Cohen, 1988). The sample size estimation was therefore based on the predicted large effect sizes for GLM for repeated measurements (f=0.4) and for *t*-tests (d=0.8), and for Pearson correlation coefficient (r=0.5) with a generally accepted statistical power of 0.80 at an alpha level of significance of 5% (Cohen, 1988). Effect sizes can be generally categorized into small (d=0.2), medium (d=0.5), and large (d=0.8). However, the sample size is underpowered to identify medium or small effect sizes.

3. Results

IPT and the control group each included 24 outpatients with schizophrenia (Fig. 1). 6 patients of the IPT group (25%) and 9 of the control group (37.5%) dropped out (chi-square=0.87, p=0.35). The patients who dropped out, did not differ in any patient characteristics or baseline assessments from those who finished the study participation ($t < 1.5$; $p > 0.14$). The reasons for dropping out were low motivation (IPT: n=5; TAU: n=5) to follow through this project (attendance rate $< 50\%$) or relapse (IPT: n=1; TAU: n=4).

The two comparison groups are near identical regarding patient characteristics (Table 1). There was no significant difference regarding age, intelligence assessed by Wechsler Adult Intelligence Scale (WAIS, Aster et al., 2006), sex, medication and duration of illness.

Baseline analysis revealed no significant differences in any outcome variable (*T*-test: $t < 1.6$; $p > 0.13$) between the two comparison groups. Regarding proximal outcome, inconsistent results could be found in neurocognitive functions. IPT patients showed significant higher effects in working memory, assessed by LNS, during therapy and highly significant effects during therapy and the follow-up period when compared to the control group. However, the two groups did not differ in verbal memory (VMT) and vigilance (CPT). Regarding social cognition, IPT patients obtained generally highly significant effects in all variables concerning

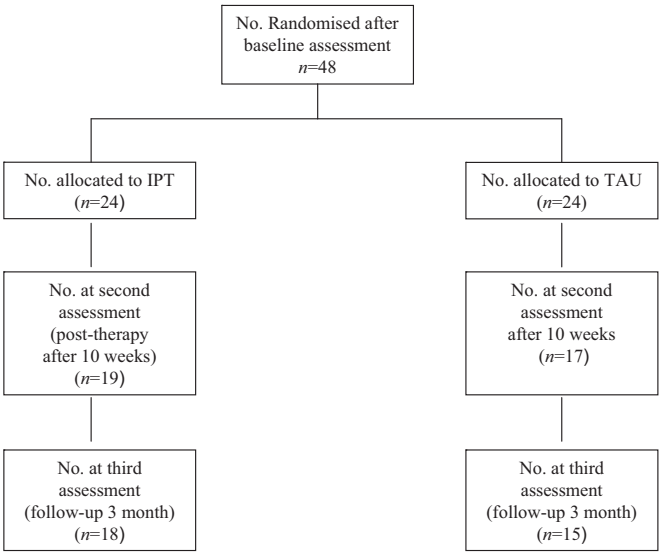

Fig. 1. Consort diagram: Flow diagram of subject progress through phases of the randomized controlled trial for the Integrated Psychological Therapy (IPT) and Treatment As Usual (TAU) group.

Table 1
Patient characteristics (N=48).

	IPT	TAU	*t/Chi. Sq*	*p*
	N=24	N=24		
	M (SD)	M (SD)		
Age	31.3 (7.2)	33.8 (6.7)	1.2	0.22
IQ (WAIS[a])	89.9 (9.4)	89.7 (7.7)	0.0	0.92
Duration of illness	5.4 (1.3)	(5.9) (1.1)	1.4	0.16
Medication (chlorpromazine equivalents)	542.1 (391.1)	512.1 (355.0)	0.28	0.78
Atypical (%)	83.3	83.3	0.0	1.0
Gender (% male)	67	67	0.0	1.0

Note:
[a] Wechsler Adult Intelligence Scale WAIS.

social perception assessed by SPS during therapy as well as during therapy and the follow-up period compared to TAU. These effects were the strongest in social perception and most robust in all assessments.

Regarding more the distal outcome, strong effects of high significance favoring IPT could be found in negative symptoms assessed by PANSS during therapy, and in negative symptoms as well as general symptoms during therapy and the follow-up period. However, no effects could be found relating to positive symptoms (PANSS) and psychosocial functioning as assessed by GAF. The PANSS score of insight showed significant superiority for IPT compared to TAU both after therapy and at the follow-up. In the assessment of the quality of life (WHOQOL), a significant effect favoring TAU was found at the follow-up (Table 2).

Pearson correlation coefficients between patient characteristics and change scores in outcome (T1–T2; T1–T3) were calculated to identify possible impacts on outcome. Only the duration of illness was significantly associated with an improvement in insight assessed by PANSS during therapy in IPT ($r=0.49$; $p<0.04$) suggesting that younger patients improved more than the older patients did. However, this effect was not evident at follow up and under TAU condition.

In addition, the calculation of effect sizes (d) for the therapy phase (T1–T2) and the therapy and the follow-up phase (T1–T3) between the IPT and the TAU group showed large effect sizes in working memory (LNS) and in social perception (SPS) during therapy, which were still evident at follow-up. Small to medium effect sizes in vigilance (CPT) and verbal memory (VMT) indicate some increased functioning over time strictly favouring IPT compared to TAU. The composite scores of neurocognition (mean of all assessed variables relating to neurocognition) were $d=0.62$ during therapy and $d=0.57$ during therapy and the follow up period. Composite scores of all cognitive assessments (neuro- and social cognition) were $d=1.70$ during therapy and $d=1.99$ during therapy and the follow up (Table 2).

Regarding more distal outcomes, large effect sizes could only be found in negative symptoms and to a lesser extent also in positive symptoms (PANSS). Effect sizes of the composite score of distal outcome variables were $d=0.56$ during therapy and $d=0.42$ during therapy and follow up. Ultimately, the mean effect of all variables reporting the overall therapy outcome, showed a large

Table 2
Proximal and distal outcome: General Linear Model (GLM) for repeated measures and effect sizes (d).

		T1	T2	T3	GLM T1-T2		Effect size T1-T2	GLM T1-T2-T3[a]		Effect size T1-T3
		M (SD)	M (SD)	M (SD)	*F*	*p*	*d*	*F*	*p*	*d*[b]
Proximal outcome										
CPT[c] commission	**IPT**	3.3 (4.2)	2.9 (7.6)	1.7 (4.1)	2.4	0.13	0.68	0.39	0.48	0.39
	TAU	2.5 (3.3)	3.3 (5.0)	3.1 (5.2)						
LNS[d]	**IPT**	13.1 (4.2)	17.9 (2.4)	17.3 (4.8)	**9.0**	***0.00***	0.95	**3.5**	***0.04***	0.80
	TAU	12.4 (4.49)	13.6 (4.9)	12.8 (4.5)						
VMT[e] recognition	**IPT**	14.1 (1.6)	14.7 (1.2)	14.6 (2.1)	0.4	0.56	0.23	0.6	0.53	0.53
	TAU	13.1 (1.7)	13.7 (1.5)	12.4 (5.3)						
SPST[f] stimulus	**IPT**	19.6 (7.3)	41.9 (11.7)	46.3 (10.2)	**21.9**	***0.00***	2.64	**31.7**	***0.00***	3.89
	TAU	15.7 (7.2)	16.1 (5.9)	14.0 (8.6)						
SPST interpretation	**IPT**	6.2 (1.1)	10.2 (1.5)	11.1 (2.2)	**27.0**	***0.00***	2.50	**15.7**	***0.00***	3.18
	TAU	5.9 (1.6)	6.3 (1.4)	6.1 (2.9)						
SPST title	**IPT**	4.1 (2.1)	11.3 (1.0)	10.7 (1.7)	**48.6**	***0.00***	3.24	**30.3**	***0.00***	3.18
	TAU	3.4 (2.2)	3.5 (2.8)	3.5 (2.9)						
Distal outcome										
PANSS[f] positive symptoms	**IPT**	25.9 (6.9)	20.1 (5.2)	17.6 (5.7)	2.9	0.09	0.43	2.6	0.08	0.44
	TAU	27.5 (6.9)	25.2 (5.0)	21.9 (5.1)						
PANSS negative symptoms	**IPT**	33.5 (4.5)	26.1 (4.3)	24.0 (4.6)	***13.6***	***0.00***	0.89	***12.0***	***0.00***	1.21
	TAU	31.0 (4.3)	30.3 (5.8)	28.9 (4.7)						
PANSS general symptoms	**IPT**	59.9 (14.3)	45.6 (9.4)	43.9 (13.8)	3.7	0.06	0.62	***5.0***	***0.01***	0.75
	TAU	59.0 (12.6)	55.5 (9.9)	52.2 (13.0)						
PANSS insight	**IPT**	4.1 (1.2)	2.9 (0.9)	2.6 (0.8)	1.7	0.20	0.62	1.9	0.16	0.57
	TAU	4.5 (1.2)	4.1 (1.2)	3.6 (1.1)						
GAF[g]	**IPT**	36.0 (10.9)	44.1 (11.5)	54.3 (11.8)	1.7	0.20	0.28	1.9	0.16	0.50
	TAU	40.5 (15.8)	43.9 (16.2)	52.5 (17.0)						
WHOQOL[h] (overall)	**IPT**	13.5 (3.7)	14.8 (3.5)	13.4 (4.4)	0.3	0.60	0.17	***4.0***	***0.03***	−0.69
	TAU	13.7 (4.0)	14.8 (2.2)	16.2 (2.7)						

Note:
[a] GLM pre and post therapy and follow up;
[b] d: Cohen's d (positive d scores indicate superiority of the experimental group IPT);
[c] Continuous Performance Test;
[d] Letter Number Span;
[e] Verbal memory Test; [f]Social Perception Test;
[f] Positive And Negative Syndrome Scale;
[g] Global Assessment and Functioning scale;
[h] World Health Organization Quality of Life. Bonferroni correction (Type I error): $\alpha'=0.004$.

effect size after therapy favouring IPT (d=0.95), that could be maintained at follow-up (d=0.97) (Table 2).

4. Discussion

This RCT represents the very first efficacy study of IPT in the Greek population.

This study focused exclusively on the cognitive part of IPT addressing neurocognition and social cognition. Therefore, cognitive functions were defined as proximal outcome. Regarding neurocognition, IPT groups only showed significant effects after therapy in working memory that could be maintained during follow-up, though not in verbal memory and vigilance. The positive effects in working memory are in line with the effects presented by the meta-analysis of Wykes and Spaulding (2011) and Wykes et al. (2011), as well as the meta-analysis of IPT studies (Mueller et al., 2013; Roder et al., 2006, 2011). But the effects in vigilance and verbal memory were contrary to the ones found in the above mentioned meta-analysis. Both found significant medium effects in verbal memory and vigilance. Besides the actual social and financial strain on Greek society, the strict outpatient setting of our study including more functional patients, may explain these results: assessment in CPT had already obtained relatively good functioning at baseline (Suwa et al., 2004). Furthermore, the small sample size may be responsible for the fact that only large effect sizes achieved the statistical level of significance (type 2 error).

Moreover, it has to be mentioned that no explicit intervention on verbal memory is included in the IPT conception and therefore has yet been conducted in the procedure. So far, verbal memory does not represent proximal outcome. On the other hand, the assessment of social perception (Fuentes et al., 2007) was very close to the content of the intervention. In consequence, the improvement of the IPT patients was by far the highest of the whole study. However, the superior effects in social perception, which were maintained during follow up, could be interpreted as the horizontal generalization of the therapy effect. The effect sizes in social perception were much higher compared to the meta-analysis on social cognitive training (Kurtz and Richardson, 2012), but reached the same level as in the evaluation study of SPS (Fuentes et al., 2007).

Regarding more distal outcome variables, IPT intervention significantly reduced negative symptoms, and to a lesser extent also showed reductions in other symptom dimensions after therapy and at follow-up. These effects are superior to those summarized by the meta-analysis of Wykes et al. (2011), where no follow-up effects were evident. In particular, the effect in our study addressing negative symptoms are of some importance in psychiatric care, since it replicates the evidence found in other IPT studies: the cognitive part of IPT group procedure appeared to reduce negative symptoms even more in middle-aged patients, and these effects could be maintained after the end of therapy (Mueller et al., 2013; Roder et al., 2011).

The reduction of negative symptoms through the neuro- and social cognitive part of IPT (i. E. cognitive remediation group approach) is more important in the background of empirically-based mediator models on schizophrenia symptomatology, suggesting that neurocognitive domains are linked to functional outcome. These connections are strongly mediated by social cognitive functions as well as by negative symptoms (Brekke and Nakagami, 2010; Green et al., 2012; Lincoln et al., 2011; Schmidt et al., 2011; Ventura et al., 2013). From a clinical point of view, the reduction of negative symptoms may support a better prognosis and improved social functioning, since negative symptoms are shown to have a negative impact on these issues (Klingberg et al., 2011).

However, no effects favouring IPT could be found in the GAF score and in the quality of life. Since the social subprograms of IPT were deleted from the therapy procedure, these results recommend the implementation of the whole integrated procedure of IPT. In other studies, only the combination of cognitive remediation with other goal-oriented interventions obtained effects in social functioning (McGurk et al., 2007; Wykes et al., 2011). In this study, patients under TAU conditions showed even better self-rating in the overall quality of life, than did IPT patients after the end of the 3 month follow-up period. This may be an artefact of the assessment. On the other hand, it may be linked with the insight of patients into the illness: poor insight has been linked to more negative attitudes toward medication, longer episodes of antipsychotic non-adherence, more frequent hospitalization, greater levels of positive and negative symptoms, lower self-esteem as well as poorer psychosocial function and quality of life (Lysaker et al., 2011). IPT patients significantly increased insight and therefore may also have developed a more realistic view of their own life, which was, in fact, much more pessimistic compared to that of the control groups.

However, in this study we have no data supporting this assumption, due to some limitations to be discussed later. We found only some data supporting an impact of the duration of illness on the improvement in insight in IPT groups during therapy but not at follow-up.

IPT could be implemented for the first time in a context of a psychiatric department of a general hospital in Greece. The coordination of the colleagues in this clinic was not always possible. Some psychiatrists were a little bit suspicious about the possibility of proposing the patients to participate in a project like that. The Director of the psychiatric department had tried to increase the motivation of the psychiatrists, in order to refer patients to the project. This study makes such context possible and attractive for further rehabilitation initiatives with IPT and further research regarding the efficacy of IPT.

Some limitations of the study have to be discussed: 1) First of all, the sample was small and only sufficient to discover large effects. The statistically underpowered sample size may have led to type II (Beta) errors: we possibly would have found more significant effects in a larger sample. 2) The follow-up phase of 3 months after the end of therapy may have been too short to really identify stable generalization effects. In comparison, the mean follow-up among IPT studies is more than 8 months (Roder et al., 2011). 3) The inclusion of TAU may have been limited in controlling unspecific group effects of IPT treatment. An active control condition may have helped to identify these effects. However, IPT is a well-evaluated therapy approach. In quantitative reviews, the superiority of goal-oriented intervention of IPT compared to unspecific group therapy, is well documented (Roder et al., 2011). Therefore, TAU is recommended as a necessary first step in evaluating the efficacy of IPT in the Greek population. 4) Regarding the assessments, the much in common MATRICS Consensus Cognitive Battery (MCCB) would have been a more appropriate instrument in measuring cognitive changes in these Greek patients. However to our knowledge, no Greek translation of MCCB is available yet.

5) Regarding more distal outcomes, it is a clear limitation to have assessed social functioning only by GAF. Although GAF is widely used and seems appropriate in samples of stable patients, it may be confused with symptom severity and may not be very sensitive for psychosocial changes (Mueller et al., 2015; Robertson et al., 2013; Startup et al., 2002). Therefore, it would have been useful to include more measures of social functioning. 6) We have only included the cognitive part of IPT in this study. To really benefit from the advantage of IPT as an integrated therapy approach in long-term treatment, it would be important to implement the complete IPT program (Roder et al., 2011).

A further goal of this project was to implement an evidence-based therapy approach such as IPT into Greek health care. In a first step we carried out the cognitive part of IPT procedure representing a cognitive remediation approach in a group setting. After the initial publication of the Greek version of IPT in 2007 (Roder et al., 2007), this study now supports evidence for the feasibility of IPT procedure in patients with schizophrenia in Greece. The relatively low drop out rate and satisfying feedback by patients suggest a positive acceptance of the treatment. It is believed that this study works well as an initiation for new intervention and research possibilities in Greek psychiatric care. Some evidence was found for proximal and distal outcome success for the cognitive part of IPT, relating to cognitive remediation. More importantly, this study supports the feasibility of IPT treatment in Greek health care.

Further RCTs of adequate sample size, together with a longer follow-up plus active control conditions should also be included in the social part of IPT, in order to improve the benefit of evidence-based integrated intervention based on cognitive remediation in IPT procedure. Further RCTs of evidenced based treatments with a larger sample size plus active control groups and longer follow up, are necessary to improve evidenced based psychiatric treatment in Greek health care.

Conflict of interest

None.

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Integrated Psychological Therapy and Treatment-Resistant Schizophrenia: Initial Findings

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Integrated Psychological Therapy and Treatment-Resistant Schizophrenia: Initial Findings

Stavroula Rakitzi and Polyxeni Georgila

Objective: The aim of this Randomized Controlled Trial (RCT) is to present the initial findings of a larger RCT study conducted internationally for the first time, regarding the hypothesis, when the Integrated Psychological Therapy (IPT) for individuals with schizophrenia is more and when it is less effective, regarding Treatment-Resistant Schizophrenia (TRS) and nontreatment resistant schizophrenia (NTRS).
Methods: Forty-eight outpatients with schizophrenia of an adult psychiatric department participated in this RCT study. Eleven outpatients of IPT and 11 of the Treatment as Usual (TAU) belong to TRS. Thirteen patients of IPT and 13 of TAU belong to NTRS. A test battery was given at baseline after therapy (10 weeks) and at 3 months' follow-up. Neurocognition, social cognition, psychopathology, and functional outcome were assessed. The General Linear Model (GLM) for repeated measurements was used. Effect sizes, z-scores, and the sign test were calculated.
Results: There was a statistical significance for verbal memory; positive, negative symptoms and general psychopathology; Global Assessment and Functioning

Stavroula Rakitzi studied psychology at the Georg-August-University of Göttingen in Germany. She holds the European Diploma of Psychology. She was trained in cognitive-behavioral psychotherapy in Athens according to EABCT Criteria. Since 2001 she is working as Diplompsychologist and Cognitive Behavioral Psychotherapist in private practice. She promotes the Integrated Psychological Therapy for patients with schizophrenia since 2006 in Greece. She is a trainer in Cognitive-behavioral Therapy and in the Integrated Psychological Therapy (IPT) in her private practice in Athens Greece. She developed the IPT postgraduate program for psychologists and psychiatrists in Greece, who has been trained in CBT. She participated as trainer in CBT and in IPT in the training program for Psychiatrists in training in the psychiatric department for adults of the General hospital G. Gennimatas in Athens Greece program from 2009-2017. She participated in many national and international conferences as a speaker, and she is an author of papers in greek and international journals and books. She is cand PhD at the university of Koblenz–Landau in Germany. She is a member of the Hellenic Society for Behavioral Research and Therapy (www.eees.gr) and of BDP. (www.bdp.org) srakitzi@gmail.com LinkedIn: gr.linkedin.com/pub/stavroyla-rakitzi/45/12b/b5 http://www.psychologenportal.de/karte/stavroylarakitzi.htm *Polyxeni Georgila* is Director of the adult psychiatric department of the general hospital "G. Gennimatas" in Athens Greece. She studied Medicine at the University of Athens and specialized in neurology-psychiatry at Eginition Hospital in Athens Greece. She has attended the program of cognitive therapy of Prof. Papakostas at Eginition. She was a member of the Mental Health Committee of the Ministry of Health in Greece. Her clinical and research interests are focussing in all the psychiatric disorders. She is the first psychiatrist in Greece, who supported the first implementation of the Integrated Psychological Therapy (IPT) in Greece. She guides the training program for Psychiatrists in training in the psychiatric department for adults of the General hospital 'G. Gennimatas" in Athens Greece. She co-developed the IPT postgraduate program for psychologists and psychiatrists in Greece, who has been trained in CBT. She is a trainer in CBT and in the IPT postgraduate program in cooperation with S. Rakitzi. She participated in many national and international conferences as a speaker, and she is an author of papers in Greek and international journals and books. She is a member of the Hellenic Psychiatric Association.polyxenigeorgila@gmail.com.

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scale (GAF) and quality of life favoring NTRS. Effect sizes showed superiority of NTRS in comparison to TRS. The sign test showed a significant improvement in Integrated Psychological Therapy treatment-resistant schizophrenia (IPTTRS) that was maintained in the follow-up, in Integrated Psychological Therapy non-treatment resistant schizophrenia (IPTNTRS) and in Treatment as Usual non-treatment resistant schizophrenia (TAUNTRS).
Conclusion: The IPT is more effective in NTRS in comparison to TRS, although IPTTRS showed some improvements, maintained at follow-up. Further RCT studies with larger samples are needed.

Schizophrenia is a clinical syndrome associated with positive and negative symptoms; cognitive, behavioral and emotional dysfunctions and with an important decline in intelligence (American Psychiatric Association (APA), 2013; Ohi et al., 2017).

Neurocognition and social cognition are the most important cognitive domains for individuals with schizophrenia (Nuechterlein & Green, 2006). About 75–90% of individuals with schizophrenia suffer from neurocognitive and social cognitive deficits (Bell, Corbera, Johanessen, Fiszdon, & Wexler, 2013; Fioravanti, Bianchi, & Cinti, 2012; Nuechterlein & Green, 2006).

The positive symptoms are independent, and their remission leads to functional recovery. The improvement of negative symptoms leads to an improvement of cognitive functions that has a positive impact on the functional outcome (Mueller, 2012). Social cognition mediates the relationship between neurocognition and functional outcome (Schmidt, Mueller, & Roder, 2011).

Integrative therapeutic interventions, which focus on cognitive, social functions, symptoms, and functional outcome have been of great interest in the last years (Mueser, Deavers, Penn, & Cassisi, 2013; Roder, Mueller, & Schmidt, 2011).

The Treatment-Resistant Schizophrenia (TRS) has been defined by the international Psychopharmacology Algorithm Project (IPAP) as: (1) no period of good functioning in the previous five years, (2) prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4–6 weeks each at doses 400-mg, equivalent of chlorpromazine or 5 mg/day risperidone, and (3) moderate to severe psychopathology, especially positive symptoms: conceptual disorganization, suspiciousness, delusions, or hallucinatory behavior. The IPAP considers continued negative or cognitive symptoms, violence, suicidality, and recurrent mood symptoms as elements of treatment refractoriness. About 30–60% of the patients with schizophrenia belong to the TRS category (Ballon & Lieberman, 2010). Howes et al. (2017) present a very interesting review regarding a new initiative for a definition of TRS.

Clozapine is recommended for TRS after two antipsychotic medications fail to lead to sufficient symptom improvement. The therapy with clozapine has on the other hand its own limitations (Ballon & Liebermann, 2010; Buchanan, 2007; Dold & Leucht, 2014; Mcilwain, Harrison, Wheeler, & Russell, 2011; Mouchlianitis, McCutcheon, & Howes, 2016; Remington et al., 2016; Suzuki et al., 2011, 2012).

Patients with TRS show more resistant cognitive symptoms than individuals with nontreatment resistant schizophrenia (NTRS) that are associated to clinical symptoms, as well as to high anticholinergic

effects because of antipsychotic treatment (Frydecka, Beszlej, Goscimski, Kiejna, & Misiak, 2016).

Psychological therapy in combination with medication is very important for individuals with TRS (Citrome, 2011). Individuals with medication-resistant psychosis have poorer prognoses, increased hospitalization, and the cost of their care is higher. Cognitive behavioral therapy (CBT) for psychosis is effective in positive and general symptoms (Burns, Erickson, & Brenner, 2014). In a five-year follow-up, the CBT group showed a more durable effect on overall and negative symptoms (Turkington et al., 2008). The CBT may be useful to reduce negative symptoms. A combination of CBT and cognitive remediation (CR) might be even more effective for the treatment of negative symptoms (Klingberg et al., 2011).

The number of studies with patients with TRS and psychotherapeutic intervention or rehabilitation and cognitive remediation is small (Seppälä, Molins, Miettunen, Hirvonen, & Corripio, 2016).

The Integrated Psychological Therapy (IPT) presents an evidence-based integrative approach for the improvement of neurocognition, social cognition, social functions and problem-solving that contributes to the rehabilitation of people with schizophrenia (Efthimiou & Roder, 2009; Mueller, Schmidt, & Roder, 2013; Rakitzi & Efthimiou, 2016a; Rakitzi, Efthimiou, & Mueller, 2016b; Roder, Brenner, & Kienzle, 2008; Roder, Brenner, Kienzle, & Efthimiou, 2007; Roder et al., 2007; Roder, Mueller, Brenner, & Spaulding, 2010; Roder, Mueller, Mueser, & Brenner, 2006; Roder et al., 2011).

The IPT is based on a hypothesis that basic cognitive deficits have a pervasive effect on social skills and social functioning (Brenner, Hodel, Roder, & Corrigan, 1992; Roder et al., 2011). The IPT begins with neurocognition (SP1: Cognitive Differentiation) and social cognition (SP2: Social perception), Communication (SP3: Verbal communication), Social skills (SP4: social skills) and finally problem-solving skills (SP5: interpersonal problem-solving) (Roder et al., 2010, 2011).

The first Randomized Controlled Study (RCT) regarding the efficacy of IPT in individuals with schizophrenia in the Greek population was recently published (Rakitzi et al., 2016b). The results are in line with the results of the meta-analyses regarding the efficacy of IPT (Mueller et al., 2013; Roder et al., 2006, 2011).

This RCT study is a part of the recent RCT study (Rakitzi et al., 2016b) and aims to examine the interaction of IPT against TAU and the history of TRS and NTRS.

This is the first RCT efficacy study with IPT concerning the above hypothesis. It aimed to specifically examine the following hypothesis: The IPT is more effective in NTRS in the proximal outcome of neurocognitive and social cognitive functions and in distal outcomes of symptom reduction and psychosocial functioning in comparison to TRS (IPT, TAU) group.

This study will probably offer new empirical data regarding the interaction of IPT against TAU and TRS against NTRS in combination with medication. It presents the initial findings of a larger RCT study to be conducted in the near future by the authors.

MATERIAL AND METHODS

This RCT study is a part of the study regarding the efficacy of IPT in Greek persons with schizophrenia (Rakitzi et al., 2016b). It was conducted between 2009–2013.

Compliance with Ethical Standards

The study design was approved by the ethical and scientific committee of the General Hospital G. Gennimatas in Athens Greece and was, therefore, performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their

inclusion in the study after the nature of the procedures had been fully explained. Details, which might disclose the identity of the subjects were omitted. The authors have complied with the APA ethical standards.

Definition of TRS in This Study

The TRS is operationalized in this study through the following criteria: no period of good functioning in the previous five years, prior non-response to at least two antipsychotic drugs of two different chemical classes for at least 4–6 weeks, each at doses 400-mg equivalents of chlorpromazine, persistent negative and cognitive symptoms (Ballon & Lieberman, 2010; Buchanan, 2007; Howes et al., 2017).

Study Population

The study was conducted with 48 Greek outpatients with schizophrenia between 2009–2013 at the psychiatric department for adults of the General Hospital "G. Gennimatas" in Athens Greece. Twenty-two outpatients belonged to the group TRS and 26 with schizophrenia belonged to the group NTRS. Eleven patients of IPT and 11 of Treatment as Usual (TAU) belonged to the group TRS and 13 of IPT and 13 of TAU belonged to the group NTRS.

Following inclusion criteria were relevant for participation in this study: Intelligence Quotient (IQ)>80, age between 20 and 50 years, duration of the disease more than 2 years, no substance abuse and no relapse 2 months before the study entry. The 48 outpatients with schizophrenia were under pharmacotherapy during the project. The medication did not change during the project.

Study Design

This study presents an RCT. Patients with schizophrenia were allocated the IPT group as experimental group and TAU as the control group, using a random draw of lots by an independent person. Patients were assessed at a baseline (T1), in the second phase 10 weeks after the intervention (T2) and in the follow-up of three months (T3) after the therapy. The Therapy by IPT and TAU lasted 10 weeks.

Therapists

The IPT groups were implemented by two therapists, experienced and very well-trained in the IPT program. A blinded rater, who did not participate in this study, administered the assessments.

Intervention

The IPT group participated in the subprograms "Cognitive Differentiation", "Social Perception" and in the first two levels of the program "Verbal Communication". The IPT groups received twice a week sessions over 10 weeks, in addition to TAU. Each therapy session lasted 60 min. The TAU is defined as standard medication, case management, and individual supportive therapy. Each of the groups consisted of eight participants. Three IPT and three TAU groups participated. Both groups were under pharmacotherapy during the whole project.

Measures

Symptoms, cognition (neurocognition and social cognition) and functional outcome present the outcome variables by studies evaluating the efficacy of IPT (Mueller et al., 2013; Roder et al., 2011).

Cognition

Intelligence declined presents a vulnerability in schizophrenia and can be evaluated by adult Wechsler-Intelligence test (WAIS) by comparing premorbid and current Intelligent Quotient (IQ) (Ohi et al., 2017). Intelligence was assessed in this study by WAIS (Aster,

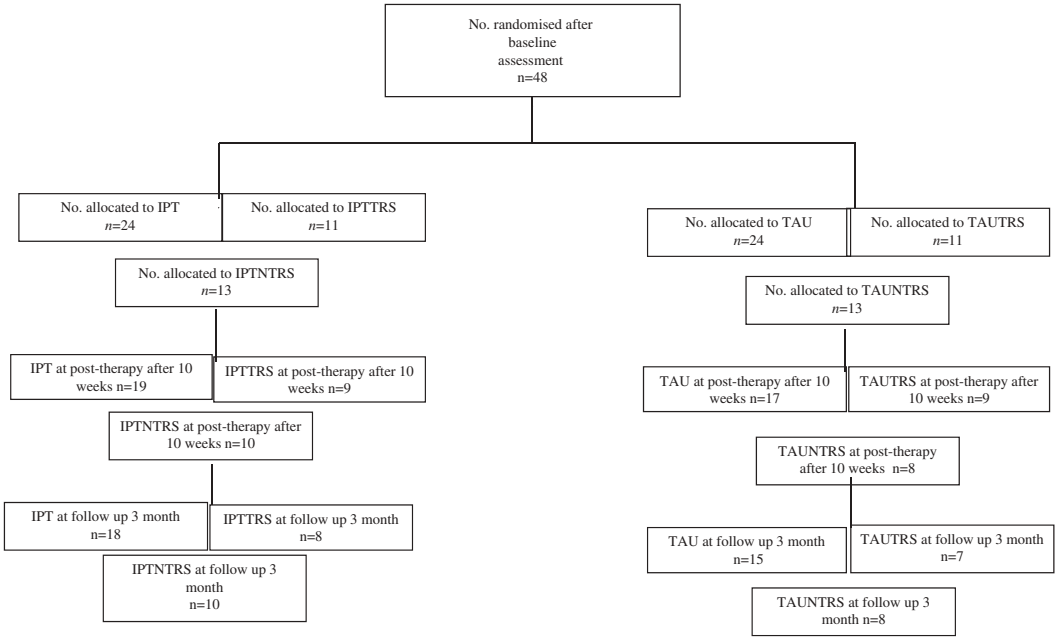

FIGURE 1. Consort diagram: Flow diagram for IPTTRS, IPTNTRS and TAUTRS, TAUNTRS group.

Neubauer, & Horn, 2006). Vigilance and attention were assessed by the Continuous Performance Test (CPT)—a reliable (.70–.90) instrument (Mass, 2002).

Working memory was assessed by the Letter–Number Span (LNS) (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Nuechterlein & Green, 2006)—a reliable instrument (.81–.78), using the Greek translation (Rakitzi, 2007a). Verbal memory was assessed by the Greek verbal memory Test (VMT)—a reliable instrument with good sensitivity, specificity and excellent internal consistency (.84-.90) (Kosmidou, 2002; Vlahou et al., 2013).

Social perception was assessed by a Greek translation of the Social Perception Scale (SPS) (Garcia, Fuentes, Ruiz, Gallach, & Roder, 2003; Rakitzi, 2007b; Ruiz, Garcia, Fuentes, & Garcia-Merita, 2005). It is a reliable instrument (.96-.1), which evaluates the three phases of the social perception program of IPT (Garcia et al., 2003).

Psychopathology

Positive, negative and general symptoms were assessed by the Greek version of the Positive and Negative Syndrome Scale (PANSS)–a reliable instrument; .82–1.0 (positive symptoms), .56-.86 (negative symptoms), .71–1.0 (general psychopathology) (Kay, Fiszbein, & Opler, 1987; Lykouras, Botsis, & Oulis, 2005).

Functional Outcome

Quality of life was assessed by the Greek version of the World Health Organization Quality of Life (WHOQOL-BREF)–a reliable instrument (.67-.81) (Ginieri-Coccosis, Triantafillou, Antonopoulou, Tomaras, & Christodoulou, 2003; Ginieri-Coccosis et al., 2012). Psychosocial functioning was assessed by the Global Assessment and Functioning scale (GAF) (American

Psychiatric Association (APA), 2004; Startup, Jackson, & Bendix, 2002).

RESULTS

The SPSS Version 13 was used for statistical analysis. The GLM for repeated measurements, t-test to analyze the empirical data. *Z*-scores and a sign test were used (Bortz & Doring, 2002). Additionally, effect sizes were calculated (Cohen, 1988). Figure 1 shows the flow-diagram of the study.

There was a significant difference regarding medication (chlorpromazine equivalents) between the groups TRS and NTRS. Table 1 shows the characteristics of the patients. Eleven patients of the IPT group (45.8%) belonged to TRS, while 13 (54.2%) belonged to NTRS. Eleven patients of the TAU group belonged to TRS (45.8%), while 13 with schizophrenia of the TAU group (54.2%) belonged to NTRS. Six patients of the group TRS (27%) take only clozapine. Seven patients (14.6%) (chi-square = 2.90; p = .08) of the group TRS and eight patients (16.7%) (chi-square = 3.84; p = .05) of the group NTRS dropped out. The reason for dropping out was low motivation (attendance rate<50%) to follow this project or relapse. Individuals with schizophrenia who relapsed were treated by psychiatrists of the adult psychiatric department and persons with schizophrenia, who showed low motivation, continued their psychiatric treatment, especially focusing on raising low motivation.

Baseline analysis revealed significant differences between the comparison groups TRS and NTRS in the following variables: AVMT10 (verbal memory) t(43) = 2.0, p = .04, Aoveralqual (overall quality of life – Quality of life) t(43) = 2.5, p = .01, Apsychealth (psychological health – Quality of life) t(43) = 2.3, p = .02 and Asocrelat (social relationships – Quality of life) t(43) = 2.2, p = .03.

Nontreatment schizophrenia group was superior in verbal memory; positive, negative symptoms and general psychopathology, functional outcome and the quality of life in comparison to TRS group. Table 2 shows the results of the General Linear Model. Bonferroni correction reduces the chances for false-positive results (type I error): α = .05.

TABLE 1. Characteristics of the Patients

	IPT (24)	TAU (24)		
	TRS (11)	NTRS (13)		
	TRS (22)	NTRS (26)	t/Chi.Sq	*p*
	M(SD)	M(SD)	TRS (11)	NTRS (13)
Age	31.3 (7.2)	33.8 (6.7)	1.2	0.22
	32.86(6.62)	32.26(7.42)	0.29	0.77
IQ (WAIS)	89.9 (9.4)	89.7 (7.7)	0.0	0.92
	88.18(7.89)	91.07(8.95)	1.17	0.24
Duration of illness (years)	5.4 (1.3)	5.9 (1.1)	1.4	0.16
	6.0(1.11)	5.38(1.29)	1.74	0.08
Medication				
(chlorpromazine equivalents)	542.1 (391.1)	512.1 (355.0)	0.28	0.78
	666.13(465.23)	409.42(209.48)	2.53	0.01
Gender (% male)	67	67	0.0	1.0
	59.1	73.1	1.04	0.30
Antipsychotics (% Atypical)	83.3	83.3	0.0	1.0
	100.0	96.2	0.86	0.35

Note: M: Mean, SD: Standard Deviation, t: test, ChiSq: chi-square test.

TABLE 2. General Linear Model (GLM) for Repeated Measures

		T1	T2	T3	GLM T1-T2		GLM T1-T2-T3	
		M(SD)	M(SD)	M(SD)	F	*p*	F	*p*
Proximal outcome								
Neurocognition								
Vigilance (Continuous Performance Test)								
CPT Omission	TRS	3.66(6.59)	3.06(5.88)	1.40(2.38)				
	NTRS	2.83(3.41)	1.55(2.52)	1.33(4.0)	0.21	0.64	0.18	0.66
Working memory (Letter Number Span)								
LNS	TRS	13.93(4. 94)	16.13(4.53)	13.53(4.64)				
	NTRS	12. 50(3. 71)	15.77(4.13)	16.66(3.42)	0.09	0.76	0.37	0.54
Verbal memory (Verbal memory Test)								
VMT10	TRS	9.40(2.97)	10.13(2.92)	10.0(4.69)				
	NTRS	10.83(2.64)	12.50(2.09)	11.50(3.12)	**7.35**	**0.01**	3.81	0.06
Social Cognition								
Social Cognition (Social Perception Scale)								
SPST								
Stimulus	TRS	16.60(7.04)	26.80(14.46)	29.93(21.06)				
	NTRS	18.88(7.72)	33.00(17.14)	33.05(17.24)	0. 63	0.43	2.35	0.13
SPST								
Interpretation	TRS	6.20(1.65)	8.46(2.47)	8.33(3.69)				
	NTRS	6.02(1.02)	8.38 (2.52)	9.16(3.46)	1.13	0.29	0.13	0.71
SPST								
Title	TRS	3.53(2.77)	8.13(4.35)	7.06(4.38)				
	NTRS	4.0(1.45)	7.44(4.54)	7.77(4.31)	0.34	0.56	0.006	0.94
Distal outcome								
Symptoms								
Positive symptoms								
Panss								
Positive symptoms	TRS	28. 13(6.17)	25.0(4.69)	22.86(5.11)				
	NTRS	25.33(7.14)	20.22(5.62)	16.83(4.88)	3.61	0.06	**6.55**	**0.01**
Symptoms								
Negative symptoms								
Panss								
Negative symptoms	TRS	34.0(6.16)	30.33(5.76)	28.60(5.42)				
	NTRS	31.0(6.07)	26.05(4.30)	24.27(4.23)	1.93	0.17	**7.37**	**0.01**
Symptoms								
General Psychopathology								
Panss								
General Psychopathology	TRS	62.06(11.09)	55.13(8.53)	55.06(12.83)				
	NTRS	55.06(12.83)	45.83(10.75)	41.55(9.84)	2.72	0.10	**7.05**	**0.01**
Symptoms								
Insight								
Panss insight	TRS	4.53(0.99)	3.66(1.17)	3.33(1.04)				
	NTRS	4.05(1.39)	3.27(1.17)	2.83(0.98)	1. 13	0.29	1.95	0.17
Functional recovery								
GAF	TRS	34.0(12.13)	37.93(9.88)	43.80(8.18)				
	NTRS	41.44(13.67)	49.11(14.42)	61.50(13.19)	**5.49**	**0.02**	**10.33**	**0.03**

(*Continued*)

TABLE 2. (*Continued*)

		T1	T2	T3	GLM T1-T2		GLM T1-T2-T3	
		M(SD)	M(SD)	M(SD)	F	*p*	F	*p*
Functional recovery								
Quality of life								
Overal quality of life	TRS	11.80(4.37)	14. 26(3.28)	12.86(4.42)				
	NTRS	15.11(2.39)	15.22(2.66)	16.22(2.73)	**4.78**	**0.03**	**6.31**	**0.01**
Functional recovery								
Quality of life								
Psychological health	TRS	12.42(3.20)	12.70(2.98)	12.99(3.16)				
	NTRS	14.22(2.38)	14.48(1.86)	14.13(1.83)	3.06	0.08	**6.85**	**0.01**
Functional recovery								
Quality of life								
Social relationships	TRS	12.28(2.89)	13.44(3.02)	12.69(3.45)				
	NTRS	13.86(2.64)	13.77(3.09)	14.53(1.78)	1.21	0.27	2.27	0.14

Note: **Bonferroni correction (Type I error): α = .05**

Pearson correlation coefficients between patient characteristics and change scores in outcomes (T1T2, T1T3) were calculated in order to find possible impacts on outcome.

IPT TRS: Sex was significantly associated with improvement in social cognition during therapy (r = 0.67; p = .04) that was not evident at follow-up and was significantly associated with improvement of general psychopathology (r = 0.73; p = .02), also evident at follow-up (r = 0.82; p = .01), suggesting that men improved more than women. The IQ was significantly associated with improvement of working memory, evident during therapy (r = 0.77; p = .01). It was significantly correlated with the functional outcome assessed by GAF, evident during therapy (r = 0.83; p = .005). Finally, it was significantly associated with improvement of verbal memory, evident at follow-up (r = 0.86; p = .005), suggesting that patients with higher IQ were better than the others.

TAU TRS: Sex was significantly correlated with quality of life (r = 0.86; p = .01) at follow-up, suggesting that men improved more than women. Age was significantly correlated with verbal memory during therapy (r = 0.71; p = .03) and at follow-up (r = 0.76; p = .04), suggesting that younger patients improved more than older patients.

Duration of illness was significantly correlated with improvement in vigilance (r = 0.74; p = .02) during therapy and also significantly correlated with working memory (r = 0.74; p = .02) during therapy, suggesting that younger patients improved more than older patients.

IPT NTRS: The IQ was significantly correlated with improvement of working memory (r = 0.77; p = .01) during therapy; it was significantly correlated with functional outcome assessed by GAF (r = 0.83, p = .005) during therapy and finally with verbal memory (r = 0.86; p = .005) at follow-up.

TAU NTRS: Sex was significantly correlated with vigilance (r = 0.75; p = .02) during therapy and at follow-up (r = 0.83; p = .01), suggesting that men were better than women. Age was correlated with vigilance at follow-up (r = 0.76; p = .02). It was also correlated with quality of life (r = 0.75; p = .03) at follow-up. The IQ was correlated with working memory (r = 0.77; p = .02) during therapy and also with functional outcome assessed by GAF during therapy (r = 0.82; p = .01) and at follow-up (r = 0.71; p = .04). Table 3 shows the effect sizes of IPT (TRS, NTRS) and TAU (TRS, NTRS).

TABLE 3. Effect Sizes between IPT (TRS, NTRS) and TAU (TRS, NTRS)

	d (T1-T2)[b]	*z*	*d*[a] (T1-T3)[b]7	*z*
Composite score neurocognition				
IPT (TRS)	0. 56	**0.33**	0. 45	0.03
IPT (NTRS)	0. 56	0.31	0. 64	0.37
TAU (TRS)	–0.10	–0.93	–0, 21	–1.09
TAU (NTRS)	0. 54	0.28	0. 70	0.46
Composite score social cognition				
IPT (TRS)	2. 99	0.70	3. 45	**0.78**
IPT (NTRS)	3. 21	0.82	3. 33	0.72
TAU (TRS)	0. 68	–0.64	–0. 37	–1.07
TAU (NTRS)	–0. 09	–1.09	0. 28	–0.75
Composite score cognition (proximal outcome)				
IPT (TRS)	1. 78	0.70	1. 95	0.68
IPT(NTRS)	1. 88	0.81	1. 99	0.71
TAU (TRS)	0. 29	–0.81	–0.29	–1.19
TAU (NTRS)	0. 22	–0.88	0. 49	–0.53
Composite score symptoms				
IPT (TRS)	0. 96	0.30	1. 16	0.14
IPT (NTRS)	1. 14	0.56 1. 57	0.60	
TAU (TRS)	0. 34	–0. 59	0. 31	–0.79
TAU (NTRS)	0. 49	–0.38	0. 83	–0.21
Composite score functional recovery				
IPT (TRS)	0. 53	**0. 45**	0. 43	–0.34
IPT (NTRS)	0. 34	0.05	0. 97	0.49
TAU (TRS)	0. 10	–0. 44	0. 42	–0. 47
TAU (NTRS)	0. 28	–0.07	0. 83	0. 24
Composite score distal outcome (symptoms, functional recovery)				
IPT (TRS)	0. 74	**0.42**	0. 80	–0.09
IPT (NTRS)	0. 74	0.40	1. 27	0.62
TAU (TRS)	0. 22	–0.61	0. 36	–0.74
TAU (NTRS)	0. 38	–0.29	0. 83	–0.04
Composite score General therapy outcome (proximal and distal outcomes)				
IPT (TRS)	1. 26	0.69	1. 37	0.00
IPT (NTRS)	1. 31	0.77	1. 63	0.00
TAU (TRS)	0. 25	–0.86	0. 03	0.00
TAU (NTRS)	0. 28	–0.78	0. 66	0.00

Note: a: Cohen's d (effect size), b: T1, T2, T3: assessment points pre and after therapy and at follow-up, **z: z-score.**

The duration of illness was significantly correlated with verbal memory (r = 0.77; p = .02) at follow-up and with quality of life (r = 0.71; p = .04) also at follow up.

Effect sizes show superiority of NTRS in comparison to TRS. The z-scores showed for IPTTRS a better outcome in Neurocognition (T1T2), social cognition (T1T3), functional recovery (T1T2) and distal outcome (T1T2).

A sign test showed the following significant results (Table 4 shows the results of the sign test):

The IPTTRS has a statistically significant median increase in Neurocognition (T1T2), social cognition (T1T2), (T1T3) and

TABLE 4. Sign Test: TRS (IPT, TAU) and NTRS (IPT, TAU)

Domain Group	Median (T1)	Median (T2)	Median (T3)	positive differences	negative differences	ties	*p* p<.05	*z*
Proximal outcome								
Neurocognition								
IPTTRS	7. 99	9. 83		9	0	0	.004	2.65
IPTNTRS	7. 54	9.43		10	0	0	.002	2.87
IPTNTRS	7. 54		9. 69	10	0	0	.002	2.87
Social Cognition								
IPTTRS	9. 0	19. 33		9	0	0	.004	2.65
IPTTRS	9. 0		19. 33	9	0	0	.004	2.65
IPTNTRS	9. 0	23. 00		10	0	0	.002	2.87
IPTNTRS	9.0		23. 00	10	0	0	.002	2.87
Distal outcome								
Symptoms								
IPTTRS	41.66		32. 0	0	9	0	.004	2.65
IPTNTRS	37. 0		27. 66	0	10	0	002	2.87
TAUNTRS	42.33		34. 66	0	6	2	.03	1.88
Functional Recovery								
IPTNTRS	18.13	20.25		9	1	0	.02	2.05
IPTNTRS	18.13		22.46	10	0	0	.002	2.87
Distal outcome								
(Symptoms & Functional Recovery)								
IPTNTRS	25.08	22.26		0	10	0	002	2.87

Note: IPTTRS: Integrated Psychological Therapy treatment-resistant schizophrenia; IPTNTRS: Integrated Psychological Therapy nontreatment resistant schizophrenia; TAUNTRS: Treatment as Usual nontreatment resistant schizophrenia; positive differences: improvement; negative differences: decrease; ties: no change.

a statistically median decrease in symptoms (T1T3) that highlights improvement. The IPTNTRS has a statistically median increase in neurocognition (T1T2), (T1T3), social cognition (T1T2), (T1T3), a significant median decrease in symptoms (T1T3), a significant median increase in functional recovery (T1T2), (T1T3) and a significant median decrease in distal outcome (T1T2) that highlights improvement. The TAUNTRS has a statistically median decrease in symptoms (T1T3) that also means improvement.

DISCUSSION

This is the first RCT study in Greece and internationally regarding the hypothesis when IPT is more and when less effective in persons with schizophrenia. In other words, the study focuses on the interaction between IPT and TAU and NTRS and TRS.

Nontreatment schizophrenia group showed better results in verbal memory; positive, negative symptoms and general psychopathology; functional outcome and the quality of life. Effect sizes show superiority of NTRS in comparison to TRS in composite scores of cognition (proximal outcome), distal outcome and the total therapy outcome. The z-scores showed superiority of IPTTRS in neurocognition, social cognition, functional recovery and distal outcome in comparison to IPTNTRS, TAUTRS, and TAUNTRS.

The sign test showed a significant improvement in IPTTRS in neurocognition, social cognition, and symptoms, a significant

improvement in IPTNTRS in neurocognition, social cognition, symptoms, functional recovery and distal outcome. Finally, the sign test showed a significant improvement in TAUNTRS in symptoms.

In other words, the main hypothesis of this RCT study is answered in the context of a first RCT study internationally regarding the question, when IPT is more effective. IPT is more effective under the circumstances of an NTRS. The IPTTRS, on the other side, also showed some improvements, which are maintained in the follow-up.

The low drop out of patients in TRS group highlights that the participation in a structured evidenced based psychotherapeutic program increases the possibility of remaining in psychotherapy.

The number of studies with patients with TRS and psychotherapeutic intervention or rehabilitation and cognitive remediation is small (Seppälä et al., 2016). Thus, this study probably offers the empirical data for health service research, and for public and private mental health in psychiatry and clinical psychology, regarding the implementation of one of the most evaluated rehabilitation programs for people with schizophrenia in TRS and NTRS. The low drop out in the IPT Group (TRS and NTRS) shows a positive acceptance of the treatment and of the ability of IPT to raise motivation and activate the resources of the patients, especially those with TRS.

This result is in accordance with studies regarding IPT (Rakitzi et al., 2016b; Roder et al., 2011)—a recovery-oriented therapy for persons with schizophrenia. Further RCT studies with larger samples are in demand.

Following limitations must be considered:

1. First, the sample was small.
2. The follow-up phase of 3 months after the end of therapy is very short. Patients with schizophrenia learn in a long-term. A better generalization effect could be discovered in a follow-up after several months.
3. We have implemented only the cognitive part of IPT. It is recommended to implement the whole IPT Program, in order to better improve the functional recovery process.

The RCT of larger sample sizes is necessary to evaluate further the impact of IPT on TRS in comparison to NTRS. Further RCTs are necessary to evaluate the impact of pharmacotherapy, cognitive behavioral therapy in combination with rehabilitation programs such as IPT on individuals with schizophrenia and TRS.

CONCLUSIONS

This is the first RCT study internationally regarding the hypothesis, when IPT is more and when less effective. The IPT is more effective in NTRS in comparison to TRS. IPTTRS showed on the other side also some improvements, maintained at follow-up. Further RCTs of larger samples are necessary. This study presents the initial results of a larger RCT study, to be conducted by the authors in the near future.

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Original Articles and Reviews

The Recovery Process for Individuals With Schizophrenia in the Context of Evidence-Based Psychotherapy and Rehabilitation

A Systematic Review

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Abstract: This systematic review aimed to evaluate the efficacy of Cognitive Behavioral Therapy (CBT), META Cognitive Therapy (MCT), Metacognitive Training (MCTR), Metacognitive Reflection and Insight Therapy (MERIT), of various rehabilitation programs and of recovery programs in schizophrenia. Medline/Pubmed was searched for studies published in English from January 2010 to August 2018, which were screened against inclusion criteria by two reviewers. The methodological quality of the included studies was evaluated by two independent raters, which are the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies and the fidelity criteria. The study included 41 RCTs and 12 case studies with n = 3,059 persons with schizophrenia. Cognitive Behavioral Therapy (CBT) proved to be superior in terms of the improvement of primary and secondary outcomes. MCT decreased positive symptoms and improved metacognitive capacity and insight. MCTR reduced positive symptoms and socially disruptive behavior. MERIT improved metacognitive capacity and insight. Rehabilitation programs were efficacious in the improvement of cognition, symptoms, and functional outcome. The recovery programs enhanced illness-management knowledge, attitudes toward medication and insights related to negative symptoms. It is recommended to combine the above evidence based psychotherapeutic interventions. Limitations of this systematic review are discussed toward the end of the essay. Some important factors have to be considered in the future have been mentioned.

Keywords: psychosis, CBT, rehabilitation, recovery, efficacy

This systematic review deals with the recovery process for individuals with schizophrenia within Rehabilitation, Cognitive Behavioral Therapy (CBT), Metacognitive Therapy (MCT), Metacognitive Training (MCTR), Metacognitive Reflection and Insight Therapy (MERIT), and Recovery Programs. First, the definitions of the recovery process will be presented. Subsequently, the above-described evidence-based psychotherapeutic interventions will be described. Then, the methods and results of this review will be described with details, and finally, results with limitations as well as future implications are discussed.

Definition of the Recovery Process

There are two viewpoints pertaining to the recovery process. The first point of view is the recovery "from" schizophrenia (recovery as an outcome); which is a point of view of the experts (Remission Working Group), which means that the person is free from psychopathology and functions very well in the community in the long term. The Presidents New Freedom Commission final report, which introduces the standpoint of the recovery of patients with schizophrenia and their families, describes the "being" in the recovery process (recovery as a process). The American Psychiatric Association accepts the recovery process, which is associated with the patient's autonomy, dignity, integration in the community, and the resumption of a normal development. (Amering & Schmolke, 2009; Bellack, 2006; Chan, Mak, Chio, & Tong, 2018; Davidson, Schmutte, Dinzeo, & Andres-Hyman, 2008; Frese, Knight, & Saks, 2009; Jose, Lalitha, Gandhi, Desai, & Nagaraja, 2015).

The above two definitions – recovery as an outcome (recovery from illness) and recovery as a process (being in recovery) (Davidson & Roe, 2007) – can be further categorized regarding the person who is responsible for the recovery process. Recovery as an outcome depends

on the evaluation of an expert (e.g., rating of the symptoms) and is called objective recovery. Recovery as a process – called subjective recovery – depends on the subjective experiences of the person suffering from a mental health illness. Objective recovery is the result of a therapy, which leads to remission of the symptoms and recovery regarding the functional outcome. Subjective recovery, on the other side, is a personal recovery, which can be different for every person. Objective and subjective recovery are related, and emotional distress is associated with subjective appraisals of recovery (Leonhardt et al., 2017). Greater subjective recovery is associated with a better quality of life, despite the manifestation of positive symptoms (Kukla, Lysaker, & Roe, 2014). Last, cure, illness management, and personal recovery present another model of recovery (Leonhardt et al., 2017).

This systematic review will focus on the objective as well as on subjective recovery (Leonhardt et al., 2017). The subjective recovery describes the point of view of persons with schizophrenia in an adequate manner.

Psychotherapy for the Recovery Process

Recovery in schizophrenia is possible with a multimodal intervention of pharmacotherapy and psychosocial interventions targets clinical remission and social functioning (Vita & Barlati, 2018). Psychotherapy must be recovery oriented (Grant, Reisweber, Luther, Brinen, & Beck, 2014; Mueser, Deavers, Penn, & Cassisi, 2013).

Recovery Programs

The Illness Management and Recovery program (IMR) has been proved to be effective in the improvement of the management of the disorder, enhancing the knowledge of the disorder, and reaching important personal goals (Dalum et al., 2018; Färdig, Lewander, Melin, Folke, & Fredriksson, 2011; Hasson-Ohayon, Roe, & Kravetz, 2007; McGuire et al., 2014; Mueser et al., 2006; Salyers et al., 2009).

The Wellness Recovery and Action Planning Program (WRAP) shows greater reduction in symptoms and higher improvement in hopefulness and the quality of life (Cook et al., 2012).

Cognitive Behavioral Therapy, Metacognitive Therapy, Metacognitive Training, Metacognitive Reflection and Insight Therapy and Rehabilitation for Individuals With Schizophrenia

Evidence-based biological (Kern, Glynn, Horan, & Marder, 2009; Leucht et al., 2013; Tandon, 2011) and psychosocial treatments (Kern et al., 2009; Mueser et al., 2013; Roder & Medalia, 2010; Roder, Mueller, & Schmidt, 2011; Wykes, Steel, Everitt, & Tarrier, 2008) – which promote recovery – are available nowadays to the scientific community.

Cognitive Behavioral Therapy (CBT) is effective in the reduction of symptoms as well as the improvement of mood and community functioning, and it is more effective in an acute psychotic episode in comparison to chronic schizophrenia; furthermore, it is effective in treatment-resistant schizophrenia (Beck, Rector, Stolar, & Grant, 2009; Burns, Erickson, & Brenner, 2014; Candida et al., 2016; Hofmann, Asnaani, Vonk, Sawyer, & Fang 2012; Johnson & Hoffart, 2018; Kern et al., 2009; Medalia, Beck, & Grant, 2019; Morrison et al., 2018; Mueser et al., 2013).

Recovery-focused CBT interventions seem to be more effective (Grant et al., 2014; Grant, Bredemeier, & Beck, 2017; Lysaker, Hamm, Hasson-Ohayson, Pattison, & Leonhardt, 2018; Mueser et al., 2013; Nowak, Sabariego, Switaj, & Anczewska, 2016).

On the other hand, CBT did not demonstrate encouraging results according to recently published meta-analyses (Hofmann et al., 2012; Jahuar et al., 2014; Kennedy & Xyrichis, 2017; Laws, Darlington, Kondel, McKenna, & Jauhar, 2018; Newton-Howes & Wood, 2013; Sarin, Wallin, & Widerlöv, 2011).

Metacognition is an essential key element for cognitive remediation (Cella, Reeder, & Wykes, 2015) and recovery (Bonfils et al., 2016; Lysaker, Hamm, et al., 2018; Lysaker, Gagen, et al., 2018). Metacognitive Approaches (MCA), Metacognitive Therapy (MCT), Metacognitive Training (MCTR), Metacognitive Interpersonal Therapy for Psychosis (MIT-P) and Metacognitive Reflection and Insight Therapy (MERIT) present effective and highly acceptable treatments (Eichner & Berna, 2016; de Jong et al., 2019; Lysaker, Gagen et al., 2018; Lysaker, Hamm, et al., 2018; Moritz, Woodward, & Balzan, 2016).

Cognitive Remediation (CR) therapy is effective in cognition-enhancing and compensatory strategies and has a greater effect when CR is combined with psychiatric rehabilitation (Kern et al., 2009; Morin & Franck, 2017; Saperstein & Kurtz, 2013; Wykes, Huddy, Cellard, Mcgurk, & Czoboor, 2011). CR, in early schizophrenia, had a non-significant effect on global cognition, a positive effect on verbal learning and memory, and a significant effect on functioning and symptoms (Revell et al., 2015).

Social cognition mediates the relationship between neurocognition and functional outcome (Kern et al., 2009; Schmidt, Mueller, & Roder, 2011), which highlights a strong association with the community functioning and the recovery process (Buonocore et al., 2018; Kurtz, Gagen, Rocha, Machado, & Penn, 2016; Kurtz & Richardson, 2012). The social cognitive training was significant in facial affect recognition skills, the theory of mind, the attributional style, positive and general symptoms, and executive functions (Kurtz & Richardson, 2012; Kurtz et al., 2016).

Integrative rehabilitation programs (Roder & Medalia, 2010; Roder et al., 2011; Mueller, Khalesi, Benzing, Castiglione, & Roder, 2017; Rakitzi, Georgila, Efthimiou, & Mueller, 2016) are preferable for the improvement of community functioning and recovery of individuals with schizophrenia.

The following conclusions can be drawn from the comparison of CR, CBT, MCT, MCTR, MIT-P, and MERIT:

CR improves cognitive deficits (neurocognition and social cognition), which enhances the improvement of symptoms and functional outcome (Roder et al., 2011; Wykes et al., 2011), whereas CBT aims to modify the content of the thoughts (Beck et al., 2009; Medalia et al., 2019). MCT changes how patients react to their thoughts and focuses on dysfunctional coping strategies, such as worry and thought suppression (Johnson & Hoffart, 2018; Lysaker, Gagen, et al., 2018; Moritz, Lysaker, Hofmann, & Hautzinger, 2018; Moritz et al., 2016), whereas MERIT activates the four domains of metacognition: self-reflectivity, understanding the other's mind, decentration, and mastery. This leads to an improved integrated sense of self and others, which enhances the personal recovery process (de Jong et al., 2019; Lysaker, Gagen, et al., 2018; Lysaker & Klion, 2017).

MCTR focuses on the cognitive biases (jumping to conclusions, attributional biases, and overconfidence in distortions), which are associated with the delusions, implementing CR, CBT, and psychoeducation in combination. MIT-P is an adaptation of Metacognitive Interpersonal Therapy (MIT) for psychosis and focuses on the modification of interpersonal schemas and metacognitive deficits in the personality (Lysaker, Gagen, et al., 2018).

All these evidence-based psychotherapies focus on the cognitive information processing and functioning. CR and MCTTR contain both the element of the rehabilitation of cognitive functions. MIT-P and MERIT focus both on the impact of metacognitive deficits on the disconnection from the interpersonal schemas.

On the other hand, there are differences between the above interventions: CR is concentrated on the improvement of neuro- and social-cognition, although the integrated programs, such as Integrated Psychological Therapy (IPT), focus also on the improvement of social problem-solving competence, which is called behavioral interventions. CBT, MCT, and MERIT focus on cognitive interventions. CBT is concentrated on how to change the content of the thoughts, whereas MCT focuses on what the persons think about their cognitions or thoughts. MERIT enhances the synthesis of information about self and others. MCTTR is a combination of rehabilitation and CBT, and lastly, MIT-P focuses on the schemas of the personality.

Jääskeläinen et al. (2013) reported that there was no evidence that recovery outcomes have improved over time. More effective treatments for people with schizophrenia must be developed.

This systematic review aims to provide a comprehensive review about the efficacy of CBT, MCT, MCTR, MERIT, Rehabilitation, and Recovery programs, which promote objective and subjective recovery in individuals with schizophrenia.

The systematic review answers the following research questions regarding the objective and subjective recovery:

Research Question 1 (RQ1): Is CBT efficacious for individuals with schizophrenia?

Research Question 2 (RQ2): Is MCT, MCTR, and MERIT efficacious for persons with schizophrenia?

Research Question 3 (RQ3): Are rehabilitation and recovery programs efficacious for persons with schizophrenia?

Material and Methods

This systematic review was conducted according to PRISMA guidelines (Liberatti et al., 2009).

Search Strategy

The electronic database PubMed/Medline was used as a source. The following keywords were used: recovery for people with schizophrenia, CBT for schizophrenia, and rehabilitation for schizophrenia. The last entry in PubMed/Medline was made in September 2018. Figure 1 illustrates the search strategy of the systematic review.

Selection Criteria

The following criteria were used to select the included studies:

- Object of the study: A CBT psychotherapeutic technique and rehabilitation program improving cognition, symptoms, functional outcome, and quality of life, which improves recovery outcomes in individuals with schizophrenia.
- Population: Patients < 18 years with the diagnosis of schizophrenia (not other schizophrenia spectrum disorders).
- Type of the study: Original scientific English language papers published in PubMed/Medline between January 2010 and August 2018, which evaluates the effectiveness and efficacy of CBT and rehabilitation programs regarding the recovery process.

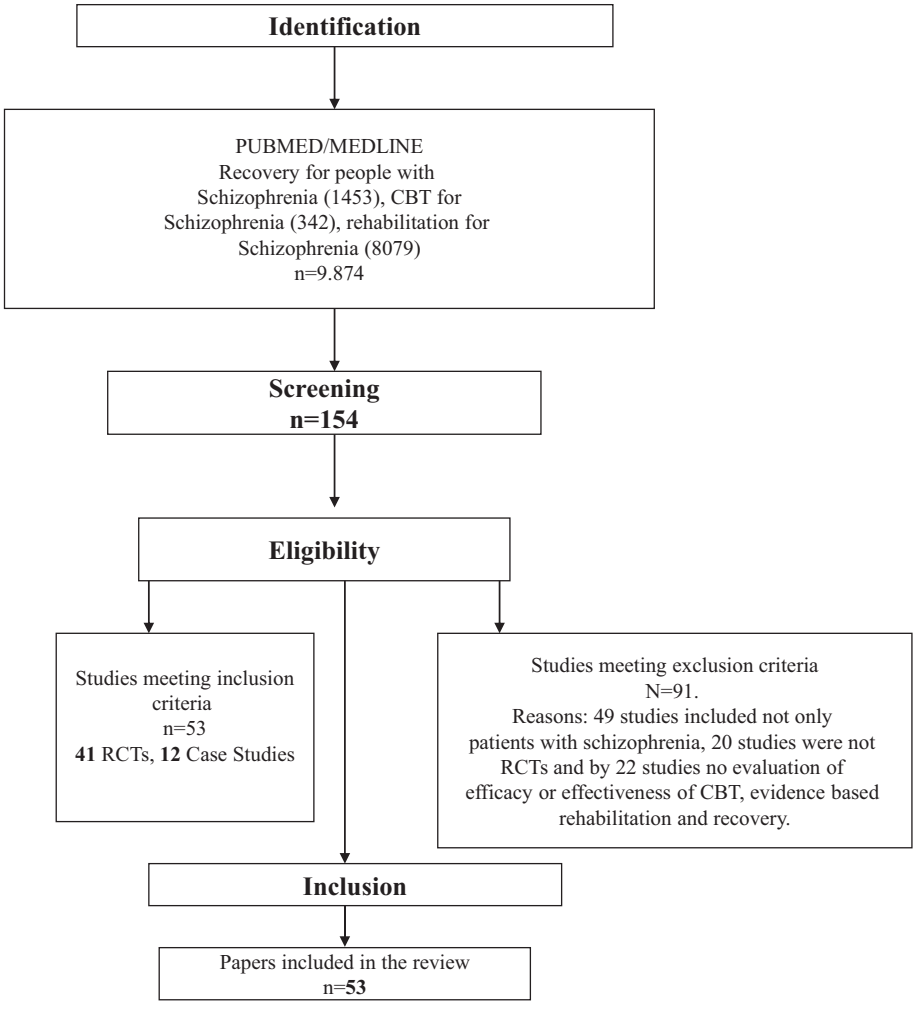

Figure 1. Flow diagram of the study selection process.

- Type of design: Randomized control studies and case studies.

Studies were excluded based on the following criteria:

(A) They were not an RCT study or a case study.
(B) They did not include only patients with schizophrenia.
(C) The target of the intervention was not efficacious or effective for CBT, MCT, MCTR, MERIT, and evidence-based rehabilitation and recovery.
(D) The papers were dissertations, unpublished papers, book chapters, letters to editors, editorials, and conference reports.

Eligibility Assessment

A trained reviewer examined all the abstracts against the selection criteria. The selected abstracts were double-checked by a second reviewer, who was blinded to the decision of the first reviewer.

Date Extraction and Data Synthesis

One reviewer extracted the appropriate information: objectives of the study, study design, study population, outcome variables, instruments, and information about the intervention.

Methodological Assessment

Included RCT studies were independently evaluated by two researchers with the Effective Public Health Practice Project (EPHPP) quality assessment tool (Thomas, Ciliska, Dobin, & Micucci, 2004).

Treatment Fidelity of the Included Studies

Included RCT and case studies were independently evaluated by the two researchers regarding the treatment fidelity, according to the Treatment Fidelity Workshop of

the National Institutes of Health Behavior Change Consortium (BBC) (Bellg et al., 2004).

Results

Study Selection

Figure 1 presents the selection process.

Characteristics of the Studies

Forty-one RCTs and 12 case studies with n = 3,059 persons with schizophrenia were included. The majority of patients (90%) were outpatients, men, and of 20–58 years. The following methods were implemented: CBT, MCT, MCTR, MERIT, CR, CR and social skills training, metacognition and social skills, vocational rehabilitation, IPT, and Integrated Neurocognitive Therapy (INT). The outcome of the therapy was to assess cognition, symptoms, functioning, insight, depression, and anxiety. Two RCTs and one case study focused on the improvement of the comorbidity (sleep disorders and pathological gambling). According to the EPHPP, 39 RCTs were qualified as strong and two RCTs as moderate. The most common reasons for evaluating them as moderate were selection bias and blinding (Table 1 and Table 2). The results regarding the efficacy of the studies are associated with objective and subjective recovery.

Effectiveness of CBT, MCT, MCTR, and MERIT Regarding the Objective and Subjective Recovery Process

Eight RCTs were included. Following RCTs demonstrated improvements in overall symptoms, general psychopathology, insight, social functioning, and comorbidity (Guo et al., 2017; Echeburua, Gomez, & Freixa, 2011, Gottlieb et al., 2017; Naeem et al., 2015; Tsiachristas, Waite, Freeman, & Luengo-Fernandez, 2018; Vohs et al., 2018). When CBT is compared to cognitive adaptation training (CAT), the outcomes were not better than CAT alone (Velligan et al., 2015). No indication of specific effects for CBT was found when CBT and CR were compared regarding the improvement of negative symptoms. It is recommended to combine CBT and CR (Klingberg et al., 2011) (objective recovery and subjective recovery).

From the above 8 studies, 7 were evaluated as strong (Echeburua et al., 2011, Gottlieb et al., 2017; Guo et al., 2017; Klingberg et al., 2011; Naeem et al., 2015; Velligan et al., 2015) and 1 as moderate (Tsiachristas et al., 2018) (Table 1).

The included 9 case studies demonstrated an improvement of cognition, functioning, insight, self esteem, and metacognitive capacity and a reduction in symptoms, avolition, sleepiness, hospitalization, and metacognitive deficits (Balzan & Galletly, 2015; Grant et al., 2014; Hamm & Leonhardt, 2016; Inchausti, Garcia-Poveda, Prado-Abrib, Ortuno-Sierra, & Gainza-Tejedor, 2017; Izuhara et al., 2018; de Jong, van Donkersgoed, Pijnenborg, & Lysaker, 2016; Leonhardt, Brenson, George, Buck, Schaieb, & Vohs, 2016; Leonhardt, Ratliff, & Vohs, 2018; Mankiewicz & Turner, 2014) (objective and subjective recovery).

Hamm and Leonhardt (2016) present an ongoing integrative psychotherapy, in which metacognition is an important therapeutic goal (subjective recovery). Psychometric tests for the evaluation of the psychotherapeutic outcome are not available (Table 2).

Effectiveness of Rehabilitation Programs Regarding the Objective and Subjective Recovery Process

Thirty-two RCTs displayed positive results regarding the recovery process: CR improved neurocognition, depression, positive and negative symptoms, vocational outcomes, insight, self esteem, functioning, and quality of life and reduced relapse rate, disorganization, and emotional distress (Bowie, McGurk, Mausbach, Patterson, & Harvey, 2012; Byrne et al., 2013; Choi et al., 2018; Garrido et al., 2013; Gharaeipour & Scott, 2012; Iwata et al., 2017; Man, Law, & Chung, 2012; Ojeda et al., 2012; Pena et al., 2016; Poletti et al., 2010; Sanchez et al., 2014; Subramaniam et al., 2014; Tao et al., 2015; Thomas et al., 2018). The effectiveness of CR in schizophrenia persists after 1 year (Deste et al., 2015). The computerized CR is not effective in schizophrenia (Gomar et al., 2015) (objective recovery).

Social Cognitive Training improved the theory of mind, emotional expression, and recognition and avolition (Bechi et al., 2013; Gaudelus, Virgile, Geliot, The GAIA/Recos Study Team, & Franck, 2016; Gil-Sanz, Fernandez-Modamio, Bengochea-Seco, Arrieta-Rodriguez, & Perez-Fuentes 2013; Palumbo et al., 2017; Sevos et al., 2018; Souto et al., 2018; Taylor et al., 2016) (objective recovery).

Integrative Rehabilitation Programs improved cognitive functions, negative and general symptoms, insight, and functioning (Mueller, Khalesi, Benzing, Castiglione, & Roder, 2017; Mueller, Schmidt, & Roder, 2015; Rakitzi et al., 2016) (objective recovery).

Vocational and psychosocial rehabilitation improved executive functions, negative symptoms, quality of life, and functioning and reduced relapse (Bio & Gattaz, 2011; Wang, Zhou, Yu, Qiu, & Wang, 2013). Cognitive-Emotional Rehabilitation (REC) and Problem-Solving Training (PST)

Table 1. Characteristics of the RCT studies

Study Country	Study design	*n*	Intervention group	Control group	Follow-up	Outcome	Quality
1. Guo et al. (2017) China	RCT	*n* = 220 n = 110 (CBT) *n* = 110 (TAU)	CBT 8 sessions	TAU	Yes	CBT better symptoms, insight, functioning	Strong
2. Echeburua et al. (2011) Spain	RCT	*n* = 44 *n* = 23 (CBT) *n* = 21 (control)	CBT and drug therapy 20 sessions	Drug therapy	Yes	CBT decrease pathological gambling	Strong
3. Gottlieb et al. (2017) USA	RCT	*n* = 37 n = 19 (CBT) *n* = 18 (TAU)	Web-based CBT 10 modules	TAU	Yes	CBT better in social functioning and knowledge about CBT	Strong
4. Naeem et al. (2015) Canada	RCT	*n* = 116 *n* = 59 (CBT) *n* = 18 (TAU)	CBT (6-10 sessions)	TAU	No	CBT better in symptoms	Strong
5. Tsiachristas et al. (2018) UK	RCT	*n* = 43 *n* = 19 (CBT) *n* = 24 (TAU)	CBT (8 sessions)	TAU	Yes	CBT improve better insomnia	Moderate
6. Velligan et al. (2015) USA	RCT	*n* = 166 *n* = 41 (CAT) *n* = 43 (CBT) *n* = 40 (CBT + CAT) *n* = 37 (TAU)	CBT, CAT, CBT & CAT (38 sessions)	TAU	Yes	CBT did not improve outcomes. CBT and CAT did not improve outcomes more than CAT alone	Strong
7. Klingberg et al. (2011) Germany	RCT	*n* = 198 *n* = 99 (CBT) *n* = 99 (CR)	CBT (20 sessions)	CR (5 sessions)	Yes	Both groups improved in negative symptoms	Strong
8. Poletti et al. (2010) Italy	RCT	*n* = 100 *n* = 58 (CRT) *n* = 42 (control)	CR (12 weeks)	Control	Yes	CRT improved better in cognitive functions and daily functioning	Strong
9. Bio and Gattaz (2011) Brazil	RCT	*n* = 112 *n* = 57 (VR) *n* = 52 (control)	VR (6 months)	Control	No	VR improved cognitive functions, negative symptoms and quality of life	Strong
10. Veltro et al. (2011) Italy	RCT	*n* = 24 *n* = 12 (CER) *n* = 12 (PST)	REC (12 months)	PST (12 months)	No	Both trainings are effective in psychopathology and social functioning. PST improved Neurocognition and CER improved social cognition	Strong
11. Bowie et al. (2012) USA	RCT	*n* = 114 *n* = 38 (CR) *n* = 38 (FST) *n* = 38 (CR + FST)	CR (24 weeks) FST (24 weeks)	CR + FST (24 weeks)	Yes	Cognitive remediation improved neurocognition. Functional competence was improved, when skills training and cognitive remediation were improved.	Strong
12. Gharaeipour and Scott (2012) Iran and USA	RCT	*n* = 42 *n* = 21 (control) *n* = 21 (CRT)	CR (40 hr)	Control	No	CR showed improvements in neurocognition, in depression and in negative Symptoms	Strong
13. Man et al. (2012) Hong Kong	RCT	*n* = 80 *n* = 27 (CCR) *n* = 23 (TCCR) *n* = 30 (control)	CCR (12 sessions) TCR (12 sessions)	Control	Yes	CCR and TCR improved better neurocognition and vocational outcomes	Strong

(Continued on next page)

Table 1. (Continued)

Study Country	Study design	*n*	Intervention group	Control group	Follow-up	Outcome	Quality
14. Garrido et al. (2013) Spain	RCT	*n* = 67 *n* = 38 (CR) *n* = 29 (control)	CR (48 sessions)	Control	No	CR improved in neurocognition, quality of life and self esteem	Strong
15. Byrne et al. (2013) Australia and China	RCT	*n* = 14 (CRT) *n* = 31 *n* = 17 (TAU)	CR (12. 78 sessions)	TAU	No	CR improved attention, positive and negative symptoms	Strong
16. Tao et al. (2015) China	RCT	*n* = 86 *n* = 44 (CRT) *n* = 42 (control)	CR (12 weeks)	Drug therapy		CR reduced the relapse, improved the employment rate and decreased the discharged time	Strong
17. Pena et al. (2016) Spain	RCT	*n* = 107 *n* = 52 (REHACOP) *n* = 52 (control)	REHACOP (39 sessions)	Occupational therapy	No	REHACOP improved neurocognition, social cognition, negative symptoms and functional disability	Strong
18. Ojeda et al. (2012) Spain	RCT	*n* = 93 *n* = 47 (REHACOP) *n* = 46 (control)	REHACOP (36 sessions)	Occupational therapy	No	REHACOP improved in cognition, in positive symptoms, in functioning and in insight	Strong
19. Wang et al. (2013) China	RCT	*n* = 140	Psychosocial rehabilitation (6 months)	Drug therapy	Yes	PR decreased relapse and improved symptoms and social functioning	Strong
20. Iwata et al. (2017) Japan	RCT	*n* = 60 *n* = 29 (CR) *n* = 31 (TAU)	CR (12 weeks)	TAU	No	CR improved neurocognition, interpersonal relationships and work skills	Strong
21. Sanchez et al. (2014) Spain	RCT	*n* = 92 *n* = 38 (REHACOP) *n* = 54 (control group)	REHACOP (36 sessions)	TAU	No	REHACOP improved in neurocognition, negative symptoms and functioning	Strong
22. Gomar et al. (2015) Spain	RCT	*n* = 130 *n* = 43 (CR) *n* = 44 (CC) *n* = 43 (TAU)	CR (48 sessions) CC	TAU	No	Computerized CR is not effective in schizophrenia	Strong
23. Gharaeipour and Scott (2012) Iran and USA	RCT	*n* = 42 *n* = 21 (CR) *n* = 21 (TAU)	CR (40 hr)	TAU	No	CR improved cognition and decreased symptoms	Strong
24. Subramaniam et al. (2014) USA	RCT	*n* = 30 *n* = 15 (CR) *n* = 13 (CG) *N* = 12 (TAU)	CR (80 hr) CG (80 hr)	TAU	Yes	CR improved working memory and increased brain activity	Strong
25. Kurtz et al. (2015) USA	RCT	*n* = 64 *n* = 32 (CR + SST) *n* = 32 (control + SST + control)	CR (50 hr)	Control	No	CR improved in neurocognition and empathy	Strong
26. Deste et al. (2015) Italy	RCT	*n* = 54 *n* = 15 (IPT) *n* = 22 (CR) *N* = 17 (TAU)	IPT(CT) CR	TAU	Yes	The effectiveness of CR persists after 1 year	Strong

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Table 1. (Continued)

Study Country	Study design	*n*	Intervention group	Control group	Follow-up	Outcome	Quality
27. Thomas et al. (2018) USA	RCT	*n* = 46 *n* = 24 (TCR) *n* = 22 (TAU)	TCR 40 hr	TAU	No	TCR improved verbal learning and moderate auditory perception and reduced the auditory hallucinations	Moderate
28. Choi et al. (2018) Korea	RCT	*n* = 38 *n* = 19 (CR + PR) *n* = 19 (PR) *n* = 19 (TAU)	CR + PR (20–24 sessions)	TAU	No	CR improved in cognition (logical memory and executive functions)	Strong
29. Rocha and Queiros (2013) Portugal	RCT	*n* = 30 *n* = 19 (MSCT) *n* = 16 (TAU)	MSCT (18 sessions)	TAU	No	MSCT improved in social cognition in social functioning and reduced the jumping to conclusions	Strong
30. Bechi et al. (2013) Italy	RCT	*n* = 30 *n* = 19 (TOMI) *n* = 11 (TAU)	TOMI (18 sessions)	TAU	No	TOMI improved Theory of Mind abilities	Strong
31. Souto et al. (2018) Spain	RCT	*n* = 61 *n* = 30 (ET) *n* = 31	ET (12 sessions)	TAU	No	ET improved emotion recognition and other TOMI variables	Strong
32. Sevos et al. (2018) France	RCT	*n* = 31 *n* = 16 (Cinemotion) *n* = 15 (Control)	Cinemotion (10 sessions)	TAU	No	Cinemotion improved recognition and expression of facial emotions	Strong
33. Palumbo et al. (2017) Italy	RCT pilot	*n* = 10 *n* = 5 (Social) *n* = 5 (SSANIT)	Social (40 sessions)	SSANIT (40 sessions)	No	Social improved social cognition and avolition	Strong
34. Gil-Sanz et al. (2013) Italy	RCT	*n* = 44 *n* = 20 (PECS-SCT) *n* = 24 (control)	PECS-SCT (28 sessions)	Control	No	No PECS improved theory of mind and emotion recognition	Strong
35. Taylor et al. (2016) UK	RCT	*n* = 36 *n* = 21 (SCIT) *n* = 15 (TAU)	SCIT (16 sessions)	TAU	No	SCIT improved facial affect recognition. SCIT is effective in a forensic ward setting	Strong
36. Gaudelus et al. (2016) France	RCT	*n* = 40 *n* = 21 (GAIA) *n* = 19 (RECOS)	GAIA (30 sessions)	RECOS (30 sessions)	No	GAIA improved facial emotion recognition, symptoms and social functioning	Strong
37. Mueller et al. (2017) Switzerland	RCT	*n* = 156 *n* = 81 (INT) *n* = 75 (TAU)	INT (30 sessions)	TAU	Yes	INT improved neurocognition social cognition and functioning	Strong
38. Mueller et al. (2017) Switzerland	RCT	*n* = 61 *n* = 28 (INT) *n* = 33 (TAU)	INT (30 sessions)	TAU	Yes	INT improved in attention and in functioning	Strong
39. Rakitzi et al. (2016) Greece	RCT	*n* = 48 *n* = 24 (IPT) *n* = 24 (TAU)	IPT (20 sessions)	TAU	Yes	IPT improved in working memory, in social cognition, in symptoms and in insight	Strong
40. Lin et al. (2013) Taiwan	RCT	*n* = 97	IMR	TAU	Yes	IMR improved illness management knowledge, attitudes toward medication insight and negative symptoms	Strong

(Continued on next page)

Table 1. (Continued)

Study Country	Study design	*n*	Intervention group	Control group	Follow-up	Outcome	Quality
41. Vohs et al. (2018) USA	RCT	*n* = 20 *n* = 10 (MERIT) *n* = 10 (TAU)	MERIT (20 sessions)	TAU	No	MERIT improved Insight	Strong

Note. CBT = Cognitive Behavioral Therapy; CR = Cognitive Remediation; CAT = Cognitive Adaptation Training; IPT = Integrated Psychological Therapy; PST = Problem-Solving Training; SST = Social Skills Training; CAT = Cognitive Adaptation Training; CCR = Computer Assisted Cognitive Rehabilitation Training; REC = Cognitive Emotional Rehabilitation Training; FST = Functional Adaptation Skills Training; RCT = Randomized Controlled Trial; TAU = Treatment as Usual; TCCR =Therapist Assisted Cognitive Rehabilitation; VR = Vocational Rehabilitation.

Table 2. Characteristics of the case studies

Study Country	Study design	*n*	Intervention	Outcome
1. Mankiewicz and Turner (2014) UK	Case study	1	Cognitive behavioral therapy (CBT) 16 sessions	CBT improved delusional appraisals of auditory hallucinations and comorbid anxiety
2. Grant et al. (2014) USA	Case study	1	CBT 70 sessions	CBT improved psychosocial functioning and neurocognitive performance, reduced positive symptoms and avolition and contributed to an avoidance of hospitalization
3. Izuhara et al. (2018) Japan	Case study	1	CBT-insomnia 8 sessions	CBT improved sleep. This decreased hallucinations and improved concentration
4. Inchausti et al. (2017) Spain	Case study	1	Metacognition oriented social skills training (MOSST) 16 sessions	The social acceptability of the patient's behavior has been improved and its disruptive behavior has been decreased
5. de Jong et al. (2016) The Netherlands	Case study	1	Meta cognitive therapy 12 sessions	The therapy improved the metacognitive capacity
6. Balzan and Galletly (2015) Australia	Case study	1	Meta cognitive therapy 4 sessions	The therapy improved clinical insight and decreased delusions
7. Levaux et al. (2012) Belgium	Case study	1	Goal Management Training 16 sessions	GML improved executive functions and self-esteem
8. Quee et al. (2012) The Netherlands	Case study	2	Cognitive Adaptation Training (CAT) 8 months	CAT improved functional outcome
9. Peyroux and Franck (2016) France	Case study	2	RC2S 14 sessions	RC2S improved social cognition and functioning
10. Leonhardt et al. (2016) USA	Case study	1	MERIT 72 sessions	MERIT improved metacognitive deficits
11. Leonhardt et al. (2018) USA	Case study	1	MERIT (in first episode psychosis)	MERIT improved metacognitive deficits
12. Hamm and Leonhardt et al. (2016) USA	Case study	1	Integrative recovery psychotherapy (IRP) (Interpersonal & MERIT) an ongoing psychotherapy	IRP improved metacognition

led to significant improvement in psychopathology and social functioning. PST improved planning and memory and REC improved theory of mind and emotion recognition (Veltro et al., 2011) (objective recovery).

A computer-assisted CR with a standardized program of social skills training (SST) group significantly improved attention, working memory, and empathy (Kurtz, Mueser, Thime, Corbera, & Wexler, 2015) (objective recovery). The metacognitive and social cognition training (MSCT) demonstrated significant improvement in the theory of mind, social perception, emotion recognition, and social functioning (Rocha & Queiros, 2013) (objective and subjective recovery).

From the above 31 studies, 30 were evaluated as strong and 1 (Thomas et al., 2018) as moderate (Table 1).

The following 3 case studies – in which a rehabilitation program was implemented – showed an improvement in executive functions, self esteem, social cognition, and functioning (Levaux et al., 2012; Quee et al., 2012; Peyroux & Franck, 2016) (Table 2) (objective recovery).

Effectiveness of Recovery Programs Regarding the Objective and Subjective Recovery Process

The following RCT evaluated the efficacy of Illness Management and Recovery (IMR) in patients with schizophrenia. Participants in the IMR Group exhibited greater improvement in illness-management knowledge, attitudes toward medication, insight, and negative symptoms at post-treatment at the follow up (Lin et al., 2013). The above study (Lin et al., 2013) was evaluated as strong (Table 1) (objective and subjective recovery).

Treatment Fidelity of the RCT and Case Studies

The following conclusions can be drawn considering the fidelity elements-study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills (Bellg et al., 2004):

(1) Recovery (RCT): Lin et al. (2013) (IMR) included a tool that evaluates the adherence of the clinician, which facilitates the IMR program (delivery of the treatment). Other fidelity elements were thoroughly taken into consideration.
(2) CBT-MERIT (RCTs): Guo et al. (2017) described fidelity in their study regarding providers training and treatment delivery. The other fidelity elements were considered in an appropriate way. Echeburua et al. (2011), Gottlieb et al. (2017), Tsiachristas et al. (2018), Velligan et al. (2015), and Klingberg et al. (2011) followed thoroughly the fidelity criteria. Naeem et al. (2015) and Vohs et al. (2018) fulfilled the fidelity criteria but included no follow-up; thus, the improvement of Enactment of Treatment Skills was not very clear.
(3) Rehabilitation (RCTs): All included RCTs, which contain a rehabilitation program, fulfill the fidelity criteria. The RCTs include only a post-treatment evaluation but not a follow-up evaluation (Table 1) could have a better impact on the improvement of Enactment of Treatment Skills (Bechi et al., 2013; Bio & Gattaz, 2011; Byrne et al., 2013; Choi et al., 2018; Garrido et al., 2013; Gaudelus et al., 2016; Gharaeipour & Scott, 2012; Gil-Sanz et al., 2013; Gomar et al., 2015; Iwata et al., 2017; Kurtz et al., 2015; Ojeda et al., 2012; Palumbo et al., 2017; Pena et al., 2016; Rocha & Queiros, 2013; Sanchez et al., 2014; Sevos et al., 2018; Souto et al., 2018; Taylor et al., 2016; Thomas et al., 2018; Veltro et al., 2011).
(4) Case studies (CBT, MCT, MCTR, MERIT, and Rehabilitation): Balzan and Galletly (2015), Peyroux and Franck (2016), and Grant et al. (2014) followed the fidelity criteria thoroughly. Mankiewicz and Turner (2014), Izuhara et al. (2018), Leonhardt, Brenson, et al. (2016), Leonhardt, Ratliff, and Vohs, 2018, Levaux et al. (2012), and Quee et al. (2012) followed the fidelity criteria thoroughly; they included post-treatment but no follow up, which could show better the improvement of Enactment of Treatment Skills. Inchausti et al. (2017) followed some of the fidelity criteria, specifically the design of the study, provider training, and delivery of the treatment. The evaluation of the outcome is not clear, and there is no follow-up evaluation. De Jong et al. (2016) fulfilled the design of the study, provider training, and delivery of the treatment. The evaluation of the outcome was not clearly presented and no follow up was being proceeded. Hamm and Leonhardt (2016) present an ongoing study.

Discussion

In this systematic review, we provide a review regarding the efficacy of CBT, MCT, MCTR, MERIT, Rehabilitation, and Recovery Programs, which promote objective and subjective recovery in individuals with schizophrenia. Fifty-three studies were included: 41 RCTs and 12 case studies.

CBT showed improvement in symptoms and general psychopathology, cognition, functioning, insight, and comorbid disorders, such as sleep disorders and pathological gambling, which decrease the quality of life and increase psychotic symptoms (objective recovery).

Deficits in metacognition have a negative impact on schizophrenia as well as on the individual's ability to take responsibility for its personal recovery process (Lysaker, Gagen et al., 2018). Metacognitive approaches (MCT, MCTR, and MERIT) improve metacognitive deficits enhancing awareness of cognitive processes, self-understanding and self management (Lysaker, Hamm, et al., 2018). MERIT enhances a kind of recovery, which is personally meaningful and self-directed (Lysaker, Hamm, et al., 2018). In other words, metacognitive treatments are associated with the objective as well as with the subjective recovery.

MCT was effective regarding the improvement of metacognitive capacity and clinical insight and reduced positive symptoms (Balzan & Galletly, 2015; de Jong et al., 2016) (objective and subjective recovery).

MCTR decreased the disruptive social behavior in combination with social skills training (Inchausti et al., 2017) and improved social cognition as well as social functioning decreasing positive symptoms (jumping to conclusions) in

combination with social cognition training (Rocha & Queiros, 2013) (objective and subjective recovery).

MERIT improved insight and metacognitive deficits (Hamm & Leonhardt, 2016; Leonhardt, Brenson, et al., 2016; Leonhardt, Ratliff, & Vohs, 2018; Vohs et al., 2018) (objective and subjective recovery). The concept of ongoing Integrative psychotherapy of Hamm and Leonhardt (2016) needs further replication with the evaluation of the psychotherapy outcome in an evidence-based context.

CR, social-cognitive training, and integrative rehabilitation programs are efficacious for the improvement of cognition (neuro-cognition and social-cognition), symptoms, and functioning (objective recovery).

Integrative programs are preferable due to better generalized effects (Bowie et al., 2012; Penades et al., 2012; Roder et al., 2011) (objective recovery).

IMR showed better improvement in illness-management knowledge, attitudes toward medication, insight, and negative symptoms (Lin et al., 2013) (objective and subjective recovery).

It is recommended to combine CBT with CR (Klingberg et al., 2011; Penades et al., 2012). CBT and CR together better improve the negative symptoms (Klingberg et al., 2011).

Majority of the included studies have taken into consideration the fidelity criteria (Bellg et al., 2004). It is recommended to address the fidelity criteria in every study directly, which was not the case in all the studies. A follow-up evaluation after post-treatment could provide more evidence regarding the enactment of treatment skills. Twenty-four of the included RCTs did not include a follow-up evaluation (see Table 1), whereas 3 of the case studies did (Balzan & Galletly, 2015; Grant et al., 2014; Peyroux & Franck, 2016).

The results of this systematic review are in line with other studies, which proved the efficacy of CBT, MCT, MCTR, MERIT, rehabilitation, and recovery programs, focusing on objective and subjective recovery (de Jong et al., 2019; Hofmann et al., 2012; Burns et al., 2014; Eichner & Berna, 2016; Lysaker, Hamm, et al., 2018; Lysaker, Gagen et al., 2018; Moritz et al., 2016; Roder et al., 2011; Mueller et al., 2013; Mueser et al., 2006; Wykes et al., 2011; Kurtz & Richardson, 2012; Kurtz et al., 2016).

More effective treatments for people with schizophrenia must be developed (Jääskeläinen et al., 2013).

There are some factors, which have to be probably considered by studies regarding the efficacy of CBT, MCT, MCTR, MERIT recovery, and rehabilitation and which can contribute to the improvement of recovery outcomes:

Are the therapists well trained and experienced? Cognitive dysfunctions of the persons with schizophrenia contribute to the fact that these people need more time to learn and implement into their daily routine. Therefore, it could be wiser to offer long-term CBT and rehabilitation, as suggested by Grant et al. (2014), who offer 70 sessions. Additionally, it is recommended to offer long-term follow ups to evaluate this learning process. Last, the combination of CBT, MCT, MCTR, MERIT, and rehabilitation programs could be probably a better and more effective strategy for long-term advantages for a chronic disease, such as schizophrenia.

The recovery programs, such as the IMR, enhance the recovery process directly, whereas CBT, MCT, MCTR, MERIT and rehabilitation activate the recovery indirectly. Does being given the combined implementation of IMR with CBT, MCT, MCTR, MERIT, and rehabilitation in the long term more advantages to persons with schizophrenia? This combination could probably increase the efficacy of the interventions.

More combinations of recovery-oriented interventions (Grant et al., 2014; Mueser et al., 2013) are probably required. In other words, more interventions, in which the evaluation of objective as well as subjective recovery is being proceeded, are probably on demand.

Our systematic review has its own limitations:

- The focus of published studies is in the period 2010–2018.
- A meta analysis will give better answers regarding the efficacy of CBT, MCT, MCTR, MERIT, rehabilitation programs, and recovery programs or the combination of all of them.

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