Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Does Integrated Neurocognitive Therapy (INT) reduce severe negative symptoms in schizophrenia outpatients?

Daniel R. Mueller [a,*], Zahra Khalesi [a], Valentin Benzing [a,b], Clelia I. Castiglione [a], Volker Roder [a,*]

[a] University Hospital of Psychiatry and Psychotherapy, University of Bern, Switzerland
[b] Institute of Sport Science, University of Bern, Switzerland

ARTICLE INFO

Article history:
Received 28 October 2016
Received in revised form 20 January 2017
Accepted 22 January 2017
Available online xxxx

Keywords:
RCT
Cognitive remediation
Group therapy
Integrated approach
Negative symptoms

ABSTRACT

Negative symptoms often inhibit the social integration of people suffering from schizophrenia. Reducing severe negative symptoms (SNS) in a clinically relevant way is a major unmet need. The aim of this study was to investigate whether Integrated Neurocognitive Therapy (INT), a group cognitive remediation therapy (CRT), reduces SNS in schizophrenia outpatients. INT was compared with Treatment As Usual (TAU) in a randomized-controlled trial (RCT). A total of 61 SNS outpatients participated in the study, 28 were allocated to the INT group and 33 to the TAU group. A test-battery was used at baseline, post-treatment at 15 weeks, and 1-year-follow-up. Remission rates of SNS after therapy were significantly higher for INT compared to TAU. A trend favoring INT was obtained at follow-up. Furthermore, INT showed significantly higher functional outcome during follow-up compared to TAU. Regarding cognition, the strongest significant effect was found in attention post-treatment. No effects between groups on more complex neurocognition and social cognition were evident. SNS outpatients seem to accept INT group intervention as suggested by the high attendance rate.

1. Introduction

The improvement of social functioning to reintegrate schizophrenia patients into social communities is one of the most important goals in psychiatric rehabilitation (Tandon et al., 2013; Robertson et al., 2013). A multitude of studies provide evidence for cognition and negative symptoms impacting social functioning (Schmidt et al., 2011; Green et al., 2012; Robertson et al., 2014; Ventura et al., 2014; Strassnig et al., 2015). Negative symptoms refer to a loss or diminution of normal function, such as expressiveness or motivation (Andreasen et al., 2005; Leucht et al., 2009; Messinger et al., 2011; Velligan et al., 2014). Within the broad term of cognition lies social cognition, the mental operations underlying social interactions (Couture et al., 2006; Schmidt et al., 2011; Green et al., 2004) and neurocognition, mental processes such as attention, verbal learning, and memory (Nuechterlein et al., 2004; Schmidt et al., 2011). There is general consensus that neurocognition and social cognition are related, but different constructs (Bozikas et al., 2004; Couture et al., 2006; Penn et al., 1997). Statistical models have demonstrated that cognition accounts for up to 25% of the variance (Schmidt et al., 2011) of social functioning, while negative symptoms account for up to 28% of the variance (Robertson et al., 2014). While both social cognition and neurocognition have been associated with functional recovery, social cognition has been proposed to mediate the relationship between neurocognition and real-world functions, otherwise termed as functional recovery (Schmidt et al., 2011; Green et al., 2012). Additionally, negative symptoms have been found to mediate the relationship between social cognitive domains and social functioning (Green et al., 2012). The associations between negative symptoms, cognition, and recovery, prompt the implementation of innovative treatments that target these factors in order to increase recovery. Moreover, negative symptoms have been a major focus of treatment due to their effects on functional recovery and resilience to interventions (Jääskeläinen et al., 2012). Recent analyses of longitudinal data suggest that negative symptoms are not as resistant as once thought and may be improved to a greater extend than it has previously been assumed (Savill et al., 2015).

Several psychosocial, behavioral, and pharmaceutical interventions have been conducted in aims to reduce negative symptoms. Pharmacological treatments have shown limited success for alleviating negative symptoms (Kirkpatrick et al., 2006; Leucht et al., 2009; Fleischhacker et al., 2014; Remington et al., 2016). A recent meta-analysis (Fusar-Poli et al., 2015) included a number of interventions for schizophrenia such as medication, Cognitive-Behavioral Therapy for Psychosis (CBTp), music therapy, and Cognitive Remediation Therapy (CRT), however none of the treatment methods reached clinically significant reductions of negative symptoms. Moreover, only a few CRT studies focused on the treatment of negative symptoms (Fusar-Poli et al., 2015;

* Corresponding authors at: University Hospital of Psychiatry and Psychotherapy, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland.
E-mail addresses: daniel.mueller@spk.unibe.ch (D.R. Mueller), roder@sunrise.ch (V. Roder).

http://dx.doi.org/10.1016/j.schres.2017.01.037
0920-9964/

Klingberg et al., 2011). There are, however, studies depicting positive effects of social skills training (SST) on negative symptoms (Bartels et al., 2014; Mueser et al., 2013), as well as successful CBTp interventions on negative symptoms (e.g. Wykes et al., 2008). While some cognitive approaches heavily focus on treating negative symptoms (e.g. Rector et al., 2005), these approaches use higher order cognitive appraisal processes such as changing maladaptive thought processes to reduce metacognitive biases that may underlie symptoms (Moritz et al., 2013). In contrast, CRT studies typically train neurocognitive and social cognitive functions such as attention, memory, executive functions, emotion processing, and Theory of Mind. An optimum treatment strategy for negative symptoms is still necessary and some researchers have chosen to use an integrative model to treat negative symptoms. A recent study investigated the effects of Motivation and Enhancement Training (MOVE, Velligan et al., 2015) on persistent primary negative symptoms (i.e., stable deficit symptoms during 5 months not caused by severe positive symptoms, depressive symptoms or medication, which refer to secondary negative symptoms). MOVE includes companion interventions based on several techniques as compensation and in-vivo strategies (Velligan et al., 2014). Pilot study results suggest some encouraging effects in the reduction of negative symptoms, but no effects were evident in the motivational factor of negative symptoms (Velligan et al., 2015). However, MOVE does not include CRT techniques that focus on cognitive functions. The inclusion of CRT techniques into an integrated comprehensive treatment concept may be a successful therapy adjunct regarding remediation of severe negative symptoms (SNS).

Measuring symptom reduction can be done in many different ways. Some studies argue that reaching a predetermined reduction rate (typically set at 20%) is enough for qualifying as significant symptoms reduction. This criterion, however, may not represent clinical remission as those who are severely ill may display statistically significant reductions in symptoms yet still be actively symptomatic and therefore not clinically remitted (Leucht, 2014). Although statistically significant reductions in symptoms are objective measures, it is also important to assess the more subjective response of "clinical remission". In order to standardize the definition of clinical remission, the Remission in Schizophrenia Working Group (RSWG) created guidelines to evaluate remission in schizophrenia across studies. The RSWG defines remission as an improvement in core symptoms that are below the threshold utilized in justifying an initial diagnosis of schizophrenia (Andreasen et al., 2005). This method of measuring remission is useful in interpreting more quantitative symptom reductions. The meta-analysis by Fusar-Poli et al. (2015) used the RSWG criteria for assessing negative symptom remissions. Due to their results indicating the lack of evidence for treatments in increasing negative symptom remission, we aim to use the same criteria for our intervention.

Integrated Neurocognitive Therapy (INT) is a CRT approach, developed by our research group, that combines neuro- and social cognition training in a group format (Mueller et al., 2015; Roder and Mueller, 2015). Due to the associations between neurocognition, social cognition, negative symptoms, and recovery, we expect that INT will significantly reduce negative symptoms as well as increase functional recovery. We also expect to find significant correlations between the measures used for neurocognition, social cognition, functional recovery, and negative symptoms. The remission criteria posed by RSWG has been used to assess clinical significance in this paper.

2. Method

2.1. Participants

Outpatients diagnosed with schizophrenia or schizoaffective disorder using DSM-IV-TR were recruited. Participants were adults between the age of 18 and 50 and were enrolled in an outpatient treatment program. Participants had to be stabilized for at least 2 months and had to show a negative symptom score of 4 (moderate symptom severity; range 1–7) in at least one of the three items on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) as defined by the RSWG (Andreasen et al., 2005). The three items included blunted affect (N1), social withdrawal (N4), or lack of spontaneity (N6). The cut-off score of 4 is directly associated with the definition of the RSWG (Andreasen et al., 2005; Leucht et al., 2007): they defined the criterion for the remission of negative symptoms as mild symptom severity (3) in these PANSS items. Exclusion criteria were neurological disorders, substance abuse according to DSM-IV-TR within 6 months before baseline assessments, and current hospitalization. All participants provided written informed consent prior to participation under protocols approved by the ethics committee at the University of Bern. Following this procedure, 63 schizophrenia outpatients with SNS were identified. Drop-out rates for the INT group during therapy and follow-up were 14.3% each. In the TAU group 6.1% dropped out during the 3-month therapy phase and 9.1% during the 9-month follow-up phase (Fig. 1).

2.2. Procedure

Outpatients were randomly assigned to INT or Treatment As Usual (TAU) groups. Therapy phase lasted 15 weeks with bi-weekly sessions (90 min each). A comprehensive battery of cognitive and functional measures was administered at baseline prior to randomization, after therapy (i.e. after 15 weeks), and after a follow-up period of 9 months (1 year after baseline assessment). Trained research assistants, who were blind to group allocation, carried out all assessments.

2.3. Intervention

INT is a manualized CRT group approach (Roder and Mueller, 2015; Mueller et al., 2015). INT incorporates all initially defined 11 neuro- and social cognitive domains defined by NIMH-Measurement and Treatment Research to Improve Cognitions in Schizophrenia (NIMH-MATRICS) into four therapy modules. Each module starts with interventions on neurocognitive domains such as attention or memory and is followed by interventions on social cognition. Each intervention on a specific cognitive domain introduces an educational tool, a compensation part in which participants learn coping strategies, a restitution part where participant practice their skills repeatedly, and in-vivo exercises. The control condition TAU was defined as standard care including a broad array of interventions for example; medication, individual therapy (with graduated psychotherapist), case-management. However, there was some overlap between the two treatment conditions: both INT and TAU patients were not allowed to take part in specific group therapies that primarily applied other CR techniques, cognitive-behavioral therapy, social skills therapy or supported employment. These criteria were instilled because these interventions may have substantial beneficial effects on neuro- and social-cognitive functions and functional outcome. That said, all patients could receive any other kinds of psychosocial interventions administered in a group setting including music therapy, art therapy, movement/dance therapy, psychoeducation, supportive and vocational counseling, and leisure time-groups.

2.4. Measures

Symptoms were measured using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987); all blinded raters received specific training and revealed high inter-rater reliability (interclass correlation coefficient ICC = 0.91). Functional outcome was assessed using the Global Assessment of Functioning Scale (GAF) of the DSM-IV was administered by the same independent and blinded raters as PANSS, again with high inter-rater reliability (ICC = 0.92). The cognitive battery consisted of tests measuring: Speed of processing, which was assessed using the Trail Making Test, Part A (TMT; Reitan, 1958);

Please cite this article as: Mueller, D.R., et al., Does Integrated Neurocognitive Therapy (INT) reduce severe negative symptoms in schizophrenia outpatients?, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.01.037