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Are the Negative Symptoms of Schizophrenia Treatable At All? A Systematic Review on Efficacy Studies for Targeted Psychological Interventions for Negative Symptoms

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Keywords
Schizophrenia · Psychosis · Negative symptoms · Treatment · Psychotherapy

Summary
Negative symptoms are among the best predictors of low levels of functioning in people with schizophrenia. Even though therapeutic interventions for negative symptoms are clearly needed, service providers often view negative symptoms as untreatable. In this article, we challenge this view by reviewing the existing efficacy studies of psychological interventions for negative symptoms. We conducted a systematic literature search and identified 36 studies that explicitly evaluated psychological interventions for negative symptoms in schizophrenia spectrum disorders. The overall pattern of findings was as follows: The effect on the motivational components of negative symptoms was largest in studies employing cognitive behavior therapy and/or social skills trainings. The effect on the expressive components of negative symptoms (i.e. blunted affect) was largest in studies using nonverbal interventions such as body-oriented psychotherapy. Cognitive remediation also had a beneficial effect on negative symptoms. However, this effect was largely unrelated to improvements in cognitive ability. Despite a dearth of methodologically sound treatment studies in the field, we could show that there are several viable therapeutic approaches to negative symptoms. Our literature overview can be used as a guide in planning treatments for people with negative symptoms.

Schlüsselwörter
Schizophrenie · Psychose · Negativsymptomatik · Behandlung · Psychotherapie

Zusammenfassung
Die Negativsymptomatik stellt einen der bedeutendsten Prädiktoren für Einschränkungen im Funktionsniveau von Menschen mit Schizophrenie dar. Allerdings wird dieser Symptombereich weitgehend als nicht behandelbar wahrgenommen. In diesem Artikel hinterfragen wir dieses Vorurteil, indem wir die Ergebnisse der existierenden Wirksamkeitsstudien für Behandlungsprogramme für Negativsymptomatik zusammenstellen. Wir beschränkten uns bei unserer systematischen Literatursuche ausschließlich auf Studien, die die Negativsymptomatik als primäres Behandlungsziel auswiesen, da vorherige Übersichtsarbeiten diesen Aspekt vernachlässigt hatten. Wir identifizierten 36 Studien, die gezielt die Wirksamkeit psychologischer Interventionen für Negativsymptomatik bei Störungen aus dem schizophrenen Formenkreis überprüften. Insgesamt stellten sich die Ergebnisse der Studien wie folgt dar: Der Behandlungseffekt für die motivationalen Komponenten der Negativsymptomatik war am größten in Studien, die kognitive Verhaltenstherapie und/oder soziale Kompetenztrainings verwendeten. Die größten Behandlungseffekte für die Affektverflachung ergaben sich in Studien zu nonverbalen Behandlungsansätzen wie der körperorientierten Psychotherapie. Auch für kognitive Remediation wurden positive Behandlungseffekte für die Negativsymptomatik gefunden, die allerdings nur teilweise mit einer Verbesserung der kognitiven Leistungsfähigkeit zusammenhingen. Obwohl es an methodisch guten Therapiestudien mangelt, zeigt unsere Literaturübersicht, dass die Negativsymptomatik psychotherapeutisch durchaus behandelbar ist. Unsere Zusammenstellung kann vor diesem Hintergrund als Entscheidungsstütze bei der Therapieplanung für Patienten mit Negativsymptomatik dienen.

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Introduction

The negative symptoms of schizophrenia have long been considered as untreatable [Buchanan, 2007]. At the same time though, in people with schizophrenia, negative symptoms are among the best predictors of low social functioning [Galderisi et al., 2014]. In what follows, we will first present the current definition of negative symptoms, in order to then explain the psychological treatment approaches to negative symptoms that currently exist and which of them are effective, according to current evidence.

Definition of Negative Symptoms in Schizophrenia

The following symptoms have been categorized as negative symptoms: blunted affect, alogia, asociality, anhedonia, and amotivation [Kirkpatrick et al., 2006; for the history of the definition of negative symptoms, see Dollfus and Lyne, 2016]. About 60% of patients with schizophrenia have at least one negative symptom of at least moderate severity [Bobes et al., 2010], with the symptoms occurring frequently and persistently in about 30% [Buchanan, 2007]. As shown in several factor analytic studies [Horan et al., 2011], two symptom domains can be distinguished within negative symptoms: *expressive negative symptoms* (blunted affect and alogia) and *motivational negative symptoms* (asociality, anhedonia, and amotivation). Patients with expressive negative symptoms stand out with a predominant reduction of their communicative expression in personal contact. Patients with motivational negative symptoms show social withdrawal and general inactivity (in both leisure time and employment). This is due to a lack of interest in these activities, as well as to a difficulty of anticipating that certain activities will be pleasurable. The two symptom areas are moderately correlated [Engel et al., 2014] and are sometimes difficult to distinguish from depressive symptoms [Trémeau et al., 2005]. The neurocognitive impairments that are frequently observed in people with schizophrenia are no longer defined as negative symptoms, according to the current conceptualization.

Negative symptoms can also occur either as primary symptoms of the disorder or as a consequence of positive symptoms or medication given to treat them [Carpenter et al., 1988]. This difference is expressed in the distinction of so-called primary and secondary negative symptoms. For instance, social withdrawal might be explained by asociality (a primary negative symptom), or by a delusion-based fear of others (secondary negative symptom).

Is There Evidence that Negative Symptoms Respond to Psychological Treatments?

There are now several meta-analyses that indeed suggest that psychological interventions have a positive effect on negative symptoms in patients with schizophrenia. Positive treatment effects have so far been demonstrated for social skills training (SST) [Kurtz and Mueser, 2008], cognitive behavioral therapy (CBT) [Wykes et al., 2008], cognitive remediation (CR) [Cella et al., 2017], an approach combining CR and SST, the Integrated Psychological Therapy Program (IPT) [Roder et al., 2011], and mindfulness-based interventions [Khoury et al., 2013]. The treatment effects of these interventions in these cases were in the medium effect-size range, which corresponds to the positive effects of CBT on positive symptoms in schizophrenia [Wykes et al., 2008]. However, 2 meta-analyses reported that most notably more recent and high-quality studies do not seem to find any significant intervention effects for negative symptoms [Velthorst et al., 2015; Wykes et al., 2008].

Apart from that, in the British therapeutic guidelines for schizophrenia agreed on by the National Institute of Health and Care Excellence (NICE) [NICE, 2014], art therapies (including body-oriented therapy as well as music therapy) are highlighted as the only consistently effective therapeutic approach for the treatment of negative symptoms.

Why a Novel Review of the Literature?

The above-mentioned meta-analyses and reviews share an important limitation: They are based primarily on studies in which not the negative but rather the positive symptoms of schizophrenia were the primary treatment target (e.g., 21 out of 23 studies in Wykes et al. [2008]). Accordingly, the therapeutic approaches were also derived mostly from psychological models of positive symptoms. It could thus be that reported effects were a result of the reduction of positive symptoms (e.g., social withdrawal decreases because the paranoid delusion decreases) and not of the reduction of actual negative symptoms. Even more problematic is that the patients in these studies were often selected on the basis of the presence of positive symptoms and therefore likely had rather mild negative symptoms. On this basis, it has so far been difficult to accurately identify interventions that are effective for negative symptoms [Aleman et al., 2016]. Furthermore, with growing recognition of the two symptom domains within negative symptoms and with the recently updated definition, a wider range of new treatment approaches has emerged, and with them initial evidence on their efficacy.

For these reasons, the present systematic review encompasses only studies of interventions targeted at the treatment of negative symptoms. Our aim was to provide an overview of the existing treatment approaches and to evaluate their efficacy. This should make it possible to verify whether negative symptoms are indeed untreatable. Moreover, we hoped to be able to provide evidence of differential efficacy of different interventions for different symptom domains, which could guide psychotherapists in treatment planning.

Methods

We conducted a systematic literature search in the databases PsycINFO and MEDLINE and used the following search string: [negative symptoms AND (schizophrenia OR psychosis OR schizophrenia spectrum disorder*) AND (treatment OR intervention OR therapy) AND (psychotherapy OR psychosocial OR (cognitive AND (behavio* OR remediation)) OR social skills)]. We also searched the bibliographies of relevant reviews and meta-analyses for further appropriate studies. We excluded non-original studies

(e.g., reviews, meta-analyses, secondary analyses) and studies that were not published in either German or English. In addition, we checked the following inclusion criteria in 2 steps:

1) Published in a peer-reviewed journal.
2) A psychological treatment effect was being studied experimentally (at least in a pre-post design).
3) The patient group being studied consisted exclusively of patients with a schizophrenia spectrum disorder (International Classification of Diseases 10 (ICD-10), coding F2).
4) One of the following validated negative-symptom assessments was used:
   a) Scale for the Assessment of Negative Symptoms (SANS) [Andreasen, 1989]
   b) Positive and Negative Syndrome Scale (PANSS) [Kay et al., 1987]
   c) Clinical Assessment Interview for Negative Symptoms (CAINS) [Horan et al., 2011]
   d) Brief Negative Symptom Scale (BNSS) [Strauss et al., 2012]
5) The intervention investigated in the study was explicitly targeted at negative symptoms, as evidenced by fulfillment of *at least one* of the following criteria:
   a) The treatment rationale was derived from findings on negative symptoms.
   b) A treatment effect for negative symptoms was explicitly hypothesized; the hypothesis was either theory or data driven.
   c) The study had established an inclusion criterion for participating patients to present with a minimum level of negative symptoms (we only distinguished between studies that used any such a criterion and studies that did not, without defining a particular criterion ourselves).

First, all titles and abstracts were screened as sensitively as possible for studies that might be included. Then, the full texts of these studies were read and assessed with regard to the inclusion criteria. The first author (M.R.) and a student assistant screened the abstracts. The first author (M.R.) then read the full texts. In case of any uncertainty regarding inclusion criteria 5a and/or 5b, a consensus was reached with the second author (M.P.).

When presenting the results, we will first give a general descriptive summary of the identified studies and then a more detailed description of the efficacy studies on the various intervention programs. We categorized the studies according to the therapeutic interventions (e.g., CBT, SST, CR). In the presentation of the results, we primarily focus on controlled studies.

Results

The flow chart in figure 1 illustrates the process of study selection. We identified 36 studies that met the inclusion criteria, and these are summarized in table 1. Of the included studies, 26 were controlled studies, and in 22 the patients were randomly assigned to the interventions (= randomized controlled trial (RCT)). On average, 66% of the participating patients were male (range 47–100%). With one exception, in all of the included studies an a priori hypothesis for a negative symptom change had been formulated; 23 studies investigated an intervention specifically focused on the concept of negative symptoms; and 14 studies used a minimum level of negative symptoms as an inclusion criterion. Twelve studies met all 3 of these criteria. All of the interventions and active control conditions reported on here were offered as a supplement to standard care (usually medication).

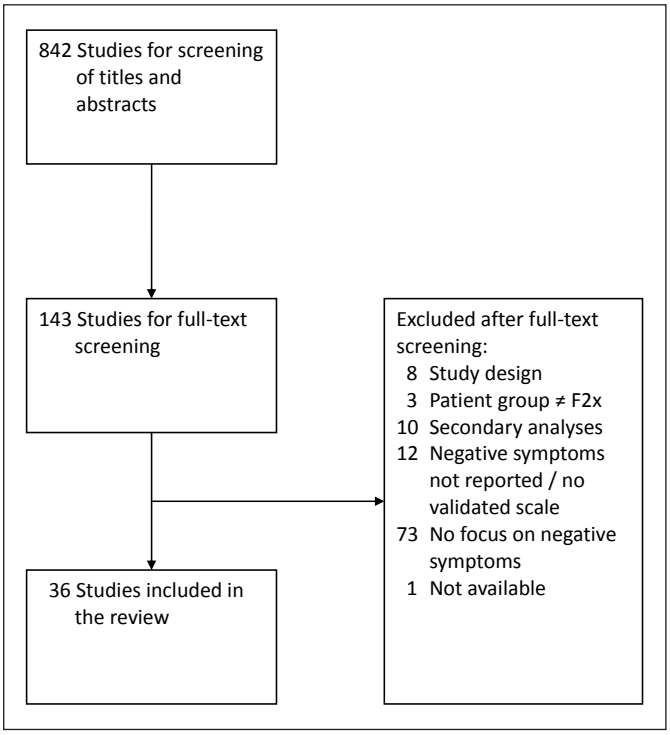

Fig. 1. Flow chart of the study selection.

Cognitive Behavioral Therapy

We identified 12 studies that examined CBT for negative symptoms. Seven of these were controlled studies, of which 5 were RCTs [Grant et al., 2012; Klingberg et al., 2011; Vauth et al., 2001, 2005; Velligan et al., 2015]. Of these, 2 compared the CBT to an active control condition, and the rest to treatment as usual. The majority of the studies (k = 9) used an inclusion criterion for negative symptoms. On average, the studies included 52 patients (SD = 52; range 6–198). The dropout rate by the end of therapy for the CBT study groups averaged about 19% (SD = 12%; range 0–35%).

In the majority of studies (especially those published since 2011), the interventions were based on the cognitive model of negative symptoms proposed by Beck et al. [2009]. In older studies [e.g., Bailer et al., 2001; Vauth et al., 2001], the interventions were derived from the cognitive therapy for depression. In the CBT studies, the interventions comprised mainly discussion techniques, role-plays, or behavioral experiments intended to identify the dysfunctional beliefs underlying negative symptoms [see Beck et al., 2009] [e.g., Grant et al., 2012; Klingberg et al., 2011]. Additionally, behavioral activation was a key element of most of the treatment programs [e.g., Mairs et al., 2011].

Table 1. Overview of the included studies, sorted according to primary therapeutic methodology

Reference	Intervention	Control	Number of sessions/ period	N EG/CG	Dropouts EG/CG[a]	NES measure	NES criterion yes/no	Result end of treatment	Follow-up
Bailer et al. [2001]	CBT	TAU	24/12 weeks	20/19	–	SANS	yes	↓NES; NES Diff EG vs. CG	stable after 3 months
Choi et al. [2016]	CBT (group)	TAU	10/5–10 weeks	23/24	4%/21%	PANSS + BNSS	yes	↓NES; ↓MOT-NES; ↓EXP-NES; NES Diff EG vs. CG	–
Favrod et al. [2015]	CBT + SST (group)	–	8/8 weeks	37/–	16%/–	SANS	yes	↓MOT-NES; Ø effect EXP-NES	–
Grant et al. [2012]	CBT	TAU	weekly/18 months	31/29	29%/31%	SANS	yes	↓MOT-NES; Ø effect EXP-NES; MOT-NES Diff EG vs. CG	–
Johns et al. [2002]	CBT (group)	–	16/20 weeks	6/–	33%/–	SANS	yes	↓MOT-NES reduction in 3 out of 4 patients; Ø effect EXP-NES	–
Klingberg et al. [2011]	CBT	active (CR)	20/9 months	99/99	9%/20%	PANSS + SANS	yes	– (Effects only reported for 3 months after end of treatment)	↓NES; Ø effect MOT-NES; ↓EXP-NES; Ø NES Diff EG vs. CG
Mairs et al. [2004]	CBT	–	max. 12/16 weeks	17/–	24%/–	PANSS	no	Ø effect NES	–
Mairs et al. [2011]	CBT	–	10–23/24 weeks	8/–	0%	SANS	yes	↓NES in 7/8 patients	↓NES stable after 6 months in 3/6 patients
Staring et al. [2013]	CBT	–	20/24 weeks	21/–	14%/–	PANSS	yes	↓NES; partial mediation by ↓dysfunctional beliefs	–
Vauth et al. [2001]	CBT (group)	active (IPT)	16/8 weeks	21/20	28%[b]	SANS	no	↓NES in CG; Ø NES Diff EG vs. CG	↓NES in EG; stable in CG after 12 months; Ø NES Diff EG vs. CG
Vauth et al. [2005]	CBT (group)	TAU	16/8 weeks	47/46	21%/39%	PANSS	no	Ø effect NES	–
Velligan et al. [2015]	CBT	TAU	40/9 months	26/25	35%/12%	CAINS + BNSS	yes	↓MOT-NES; Ø effect EXP-NES; NES Diff EG vs. CG	–
Bellucci et al. [2003]	CR	TAU	16/8 weeks	17/17	–	SANS	no	↓NES; NES Diff EG vs. CG; scarcely any effects on neurocognition	–
Farreny et al. [2013]	CR (group)	active (AG)	32/16 weeks	62[b]	–	PANSS	no	NES Diff EG vs. CG	–
Lanfredi et al. [2017]	CR	TAU	50/25 weeks	35/28	6%/–	PANSS	no	↓NES; NES Diff EG vs. CG; scarcely any effects on neurocognition	–
Rakitzi et al. [2016]	CR (group)	active (ST)	20/10 weeks	24/24	21%/29%	PANSS	no	↓NES; NES Diff EG vs. CG	stable after 3 months
Sanchez et al. [2014]	CR + SST + FI (group)	active (AG)	18/12 weeks	38/54	5%/11%	PANSS	no	↓NES; NES Diff EG vs. CG	–
Martin et al. [2016]	BPT (group)	TAU	20/10 weeks	44/24	30%/33%	SANS	no	↓NES; Ø effect MOT-NES; ↓EXP-NES; NES Diff EG vs. CG	–
Priebe et al. [2016]	BPT (group)	active (PI)	20/10 weeks	140/135	2%/4%	PANSS + CAINS	yes	Ø effect NES; Ø effect MOT-NES; ↓EXP-NES; EXP-NES Diff EG vs. CG	EXP-NES stable in EG after 6 months

Table 1. *Continued on next page*

Table 1. *Continued*

Reference	Intervention	Control	Number of sessions/ period	N EG/CG	Dropouts EG/CG[a]	NES measure	NES criterion yes/no	Result end of treatment	Follow-up
Röhricht and Priebe [2006]	BPT (group)	active (ST)	20/10 weeks	24/21	8%/33%	PANSS	yes	↓NES; Ø effect MOT-NES; ↓EXP-NES; NES Diff EG vs. CG	–
Röhricht et al. [2009]	BPT (group)	–	20/10 weeks	24/–	0%/–	PANSS	yes	↓NES; Ø correlation with process variables	stable after 4 months
Röhricht et al. [2011]	BPT (group)	–	20/10 weeks	18/–	17%/–	PANSS	yes	↓NES; ↓EXP-NES	–
Daniels [1998]	SST (group)	TAU	16/8 weeks	20/20	15%	SANS	no	Ø NES change	–
Dobson et al. [1995]	SST (group)	active (MT)	36/9 weeks	18/15	17%/13%	PANSS	no	↓NES; NES Diff EG vs. CG	EG stable after 3 months; not stable after 6 months
Galderisi et al. [2010]	SST + CR (group)	active (AG)	SST: 24 + CR: 48/24 weeks	30/30	23%/50%	SANS (EXP)	no	Ø effect EXP-NES	–
Granholm et al. [2013]	SST + CBT (group)	active (ST)	36/36 weeks	41/38	34%/16%	SANS	no	– (Inferential statistics only for 9 months after end of treatment)	↓MOT-NES; Ø effect EXP-NES; Ø NES Diff EG vs. CG
Granholm et al. [2014]	SST + CBT (group)	active (ST)	36/36 weeks	73/76	–	SANS	no	Ø effect MOT-NES; Ø effect EXP-NES	↓MOT-NES; MOT-NES Diff EG vs. CG after 12 months
Hayes et al. [1995]	SST (group)	active (DG)	36/18 weeks + 9 boosters/24 weeks	63[b]	29%[b]	SANS	no	Ø effect NES	–
Matousek et al. [1992]	SST (group)	–	16/over 16 weeks	3/–	–	SANS	yes	↓NES (but already during the baseline surveys before SST)	not stable after 4 months
Rus-Calafell et al. [2014]	SST + VR	–	16/8 weeks	15/–	20%/–	PANSS	no	↓NES	stable after 4 months
Rus-Calafell et al. [2013]	SST (group)	TAU	16/8 weeks	18/18	30%/0%	PANSS	no	↓NES; NES Diff EG vs. CG	stable after 6 months
Thara and Srinivasan [1998]	SST + FI (group)	–	–/12 months	59/–	30%/–	SANS	no	↓NES	–
Dyck et al. [2000]	PE + FI (group)	TAU	Group 2 × weekly/12 months	27/27	22%/22%	SANS	no	Ø effect NES	–
Nathans-Barel et al. [2004]	AAT	active (w/o d.)	10/10 weeks	10/10	–	SANS	no	Ø effect NES	–
Villalta-Gil et al. [2009]	AAT (group)	active (IPT)	25/12 weeks	12/9	14%/–	PANSS	no	↓NES; Ø NES Diff EG vs. CG	–
Ulrich et al. [2007]	Music therapy (group)	TAU	10/5 weeks	21/16	–	SANS	no	↓NES; ↓EXP-NES; NES Diff EG vs. CG	–

EG = Experimental/intervention group; CG = control group; Diff = difference; NES = negative symptoms; MOT-/EXP-NES = motivational/expressive negative symptoms; CBT = cognitive behavioral therapy; CR = cognitive remediation; SST = Social Skills Training; BPT = body-oriented psychotherapy; FI = family intervention; PE = psychoeducation; AAT = animal-assisted therapy; TAU = treatment as usual; IPT = integrated psychological therapy program; AG = activity group; ST = supportive therapy; PI = Pilates; MT = Social Milieu Treatment; DG = discussion group; w/o d. = same treatment without therapy dog; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; BNSS = Brief Negative Symptom Scale; CAINS = Clinical Assessment Interview for Negative Symptoms.

[a]Dropout by end of treatment.

[b]Data available only for total group.

The studies by Grant et al. [2012] and Staring et al. [2013] focused primarily on the dysfunctional beliefs described in the Beck model. In the RCT by Grant et al. [2012], there was an intervention treatment effect for amotivation, but not for other negative symptoms. In their uncontrolled study, Staring et al. [2013] showed that the symptom improvements were also associated with a change in the patients' dysfunctional beliefs. The largest study of CBT for negative symptoms, which is at the same time one of the two studies with an active control condition, was conducted by Klingberg et al. [2011]. Their treatment manual was modularized and included interventions for each of the different negative symptoms. Negative symptoms improved in this multi-centric trial with both CBT (effect size (ES) = –0.42) and CR (ES = –0.53), with no between-group differences. At the single-symptom level, there was a pre-post effect within the CBT group only for alogia (expressive negative symptom).

In more recent studies [Choi et al., 2016; Favrod et al., 2015; Velligan et al., 2015], the treatment approaches were focused more on interventions targeted specifically at etiological findings about individual negative symptoms (e.g., promoting the anticipation of pleasure). Pilot studies with varying levels of methodological precision have all found positive effects on motivational negative symptoms, ranging from medium [Favrod et al., 2015; Velligan et al., 2015] to large effect sizes [Choi et al., 2016].

To sum up, the majority of the controlled studies have found moderate positive effects of CBT on motivational negative symptoms [Bailer et al., 2001; Choi et al., 2016; Grant et al., 2012; Velligan et al., 2015], while only 2 studies found a positive effect on expressive negative symptoms [Choi et al., 2016; Klingberg et al., 2011]. Only 1 controlled study did not find a treatment effect of CBT on negative symptoms [Vauth et al., 2005]. CBT did not prove more effective in any of the studies than an active control condition. In studies with follow-up assessment, the pre-post effects achieved by CBT were stable for a period ranging from 3 months [Bailer et al., 2001; Klingberg et al., 2011] to 1 year [Vauth et al., 2001].

Cognitive Remediation

In addition to the study by Klingberg et al. [2011] (see above), we identified 5 studies that examined CR for the treatment of negative symptoms (table 1). All but one [Lanfredi et al., 2017] of these studies were RCTs. Three studies used an active control condition; the other 2 studies compared CR with treatment as usual. None of the studies used an inclusion criterion for negative symptoms. On average, 60 patients were included in the 5 studies (SD = 22; range 34–92). The dropout rate by the end of therapy in the CR study groups averaged about 13% (SD = 9%; range 5–21%).

The treatment studies on CR for negative symptoms examined interventions that followed the principles of 'Errorless Learning' with immediate feedback and shaping [see Wykes et al., 1999]. The CR interventions ranged from the mere training of neurocognitive domains such as attention, memory, and cognitive flexibility [Bellucci et al., 2003; Klingberg et al., 2011; Sanchez et al., 2014], to the integration of training in problem-solving strategies closer to everyday life, such as day-to-day planning [Lanfredi et al., 2017], to training in social perception and social problem-solving strategies [Farreny et al., 2013; Rakitzi et al., 2016].

The study by Klingberg et al. [2011] is the only study of CR for negative symptoms that was performed explicitly on patients with negative symptoms, and it is also the largest study of CR in this field. As mentioned above, Klingberg et al. [2011] found a significant moderate pre-post effect of the CR intervention on the negative symptoms and no difference from CBT. The pre-post effect was significant for both expressive negative symptoms and amotivation. The second-largest study was conducted by Sanchez et al. [2014], who integrated additional units in SST and psychoeducation for relatives in a CR group program, also finding a moderately positive treatment effect (ES = –0.48). Three other studies investigated predictors of negative symptom improvements in response to CR and found treatment effects in each case, which, however, were not or only partially predicted by improvements in neurocognition [Bellucci et al., 2003; Farreny et al., 2013; Lanfredi et al., 2017].

So far, the existing studies of CR for the treatment of negative symptoms have uniformly found significant intervention effects. However, so far there is only 1 study in which the patients were selected according to their negative symptoms, and in this study, only a pre-post effect was found. In the 2 studies that reported results for 3 months after the end of therapy, the intervention effects were stable within the respective CR study groups.

Body-Oriented Psychotherapy

Five studies examined the efficacy of body-oriented psychotherapy (BPT) for negative symptoms. Three of these were RCTs (table 1), 2 of which included an active control group. With the exception of the study by Martin et al. [2016], each of these studies established the presence of negative symptoms as an inclusion criterion. The studies included an average of 86 patients (SD = 108; range 18–275). The dropout rate in the BPT study groups averaged about 11% (SD = 12%; range 0–30%), whereas the study by Martin et al. [2016] is an outlier with a dropout rate of 30%.

All of the above-mentioned studies used the same treatment manual and thus followed the disembodiment approach to schizophrenia, according to which negative symptoms are best understood as a detachment from one's own emotions as well as from other persons in social interactions (for a more detailed description, see Martin et al. [2016]). The objectives of the interventions in the group therapies were to induce emotional states through nonverbal movement exercises, such as expressive dance, to use mindfulness exercises to raise patients' awareness in perceiving the connection among movement, physical feeling, and emotion, and to reflect upon these processes in the group.

Röhricht and Priebe [2006] found significant superiority of BPT compared to supportive therapy (ES = –0.68), which was still stable 4 months after the end of therapy (ES = –1.03). In particular, patients in the BPT group improved in expressive negative symptoms (blunted affect: ES post = 1.01; ES at 4-month follow-up = 0.93). Two recent multi-centric studies of BPT for negative symptoms examined the generalizability of these results [Martin et al., 2016;

Priebe et al., 2016]. Martin et al. [2016] found significant reductions of negative symptoms in the BPT group compared to treatment as usual at the end of the treatment (ES = –0.85). The patients in the BPT group improved particularly in blunted affect (ES = –0.65) as well as asociality (ES = –0.61). The largest sample of patients with present negative symptoms in a treatment study so far (N = 275) was investigated by Priebe et al. [2016] who compared BPT with Pilates as an active control condition. Contrary to expectations, there was hardly any treatment effect for negative symptoms, neither within the BPT group nor in comparison between BPT and Pilates. Only expressive negative symptoms were significantly more reduced with BPT than with Pilates after the end of therapy. Within the BPT group, this decrease was also stable at the 6-month follow-up. Furthermore, both of the uncontrolled treatment studies using BPT found significant pre-post treatment effects for negative symptoms. One of them [Röhricht et al., 2011] reported additional results on single symptoms and showed that expressive negative symptoms were significantly reduced after the treatment.

Thus, all 4 studies of BPT that investigated expressive negative symptoms separately found a positive treatment effect for these symptoms. Meanwhile, the majority of the studies did not find any effects for motivational negative symptoms.

Social Skills Training

We were able to identify 10 studies that primarily used SST to treat negative symptoms, 7 of which were RCTs (table 1). However, none of the controlled studies established an inclusion criterion for the presence of negative symptoms. On average, the studies included 54 patients (SD = 41; range 3–149) and the dropout rate averaged about 25% (SD = 7%; range 15–34%).

The studies' rationales were derived from the well-replicated findings showing that deficits in social skills in people with schizophrenia and prominent negative symptoms are particularly pronounced [e.g., Bellack et al., 1990]. Instructions and role-plays were common interventions that were conducted in a group setting.

Especially earlier studies did not consistently demonstrate effects of SST on negative symptoms [Dobson et al., 1995; Hayes et al., 1995; Matousek et al., 1992]. These studies used a relatively traditional SST approach, in which skills were practiced in the areas of interpersonal problem-solving, verbal and non-verbal communication, assertiveness, as well as goal setting and attainment. Another study, which investigated the effect of an SST with an additional focus on understanding the emotional communication of others [Rus-Calafell et al., 2013], showed a small to moderate positive effect on negative symptoms in a small sample, which was still stable 6 months after treatment. In a pilot study (N = 12), the same researchers successfully tested an SST variant in which some of the interpersonal exercises were conducted in virtual reality [Rus-Calafell et al., 2014]. This study found a moderate pre-post treatment effect (ES = –0.75).

Some studies investigated variants of the SST that were enhanced by different other therapeutic elements. For example, Daniels [1998] added interactive exercises derived from psychodrama to the SST. However, there were no significant changes in negative symptoms after the intervention. In 2 large-scale RCTs (N = 79 and 149), Granholm et al. [2013, 2014] investigated an extension of the SST, the Cognitive Behavioral Social Skills Training, that combined elements of CBT and SST. They found a significant decrease in motivational, but not expressive, negative symptoms in both studies. In the larger of the 2 [Granholm et al., 2014], the symptom improvements were also significant compared to the active control condition (supportive group therapy) (ES = –0,72), although the differences only became evident at follow-up 12 months after the end of treatment. A combination of SST and CR also showed no effect on expressive negative symptoms [Galderisi et al., 2010], while results for motivational negative symptoms were not reported.

Overall, the studies that used a more traditional SST have not demonstrated consistent intervention effects for negative symptoms. Positive treatment effects were found especially for enhancements that included cognitive components, such as training in emotion perception [Rus-Calafell et al., 2013], or cognitive restructuring of dysfunctional beliefs [Granholm et al., 2013, 2014]. Some of the studies assessed data for a follow-up period (table 1), in which the effects tended to remain fairly stable for up to 12 months.

Other Therapeutic Approaches

We found 2 controlled studies with small samples of animal-assisted therapy (with therapy dogs) used to target negative symptoms [Nathans-Barel et al., 2004; Villalta-Gil et al., 2009]. However, these studies, did not find any effects on negative symptoms. A study by Dyck et al. [2000] evaluated a family-centered psycho-educational approach. In this study, there were also no positive effects of the intervention compared to treatment as usual. Finally, 1 study investigated the effect of music therapy on negative symptoms [Ulrich et al., 2007]. Patients in the intervention group learned to play rhythm instruments together in the group. They improved in comparison to a treatment as usual group by the end of the treatment, especially in expressive negative symptoms.

Discussion

Our literature review has shown that some targeted interventions for negative symptoms in schizophrenia have been evaluated. CBT, CR, BPT, and SST have shown evidence of efficacy in reducing negative symptoms in varying degrees.

CBT and BPT currently provide the methodologically most convincing evidence of efficacy for the treatment of negative symptoms (i.e., both multi-centric studies and a majority of studies, in which the presence of negative symptoms was established as an inclusion criterion). Nevertheless, the findings were not completely consistent, and especially in the largest multi-centric studies in both therapeutic approaches [Klingberg et al., 2011; Priebe et al., 2016] there were deviations from the results of mono-centric studies with smaller samples. On the one hand this is to be expected, since the more rigorous methodology should control for non-specific treatment effects as much as possible. On the other hand, it is fair to say that both therapeutic approaches need to optimize treatment strategies in terms of carving out their specific effects more clearly.

New developments, which are very closely aligned with the current conceptualization of negative symptoms, offer promising prospects in CBT [Choi et al., 2016; Favrod et al., 2015; Velligan et al., 2015]. The pilot studies of these treatments have consistently reported significant treatment effects, some even with a large effect size, while many of the effects in other studies, some less well-controlled, were more in the moderate range. In the case of BPT, it will be important to identify active and non-active elements of the treatment, in hopes of developing a treatment option that is specific for expressive negative symptoms. Hence, further research on potential process variables is needed.

As we have shown, CR could also be quite an effective intervention for negative symptoms. However, to this point, it remains unknown to what extent the consistently positive effects on negative symptoms are also the result of other active components of the intervention (such as repeated experiences of social reinforcement by the therapist and of success during training). Well-controlled treatment studies are lacking here, especially with patient groups with confirmed negative symptoms.

Our review also showed that studies on the efficacy of SST for negative symptoms have so far produced inconsistent results. Certainly, the heterogeneity of the findings may also reflect the heterogeneity of the interventions used in the studies. Overall, our results thus match the meta-analytical findings mentioned at the beginning, that SST is more suitable than other interventions for treating negative symptoms [Kurtz and Mueser, 2008; Turner et al., 2014], to only a limited extent. Especially the high dropout rates indicate a need to develop SSTs that are better attuned to this patient group. Another reason why this may be important is that the SSTs' positive effects seem to be stable in the long term once established. As with CR, however, above all there is a dearth of high-quality treatment studies that investigate the efficacy of SST in patients with confirmed negative symptoms.

On the whole, different types of interventions have thus been able to demonstrate positive effects for the treatment of negative symptoms. Thus, psychological treatments seem to be principally indicated for the treatment of the negative symptoms of schizophrenia. This is demonstrated not least by the fact that patients who received 'treatment as usual' usually showed no spontaneous symptom improvement [Choi et al., 2016; Daniels, 1998; Dyck et al., 2000; Lanfredi et al., 2017], and in some cases even significant exacerbations [Bellucci et al., 2003; Martin et al., 2016; Ulrich et al., 2007; Velligan et al., 2015].

In addition to the finding of a principal indication for psychotherapy for negative symptoms, our analysis has shown that therapeutic interventions designed to correct low expectations of self-efficacy (CBT, CBT + SST, possibly CR) are most successful when it comes to improving motivational negative symptoms. By contrast, therapeutic interventions that promote the connection of physical feeling and emotion (BPT, music therapy) seem to be successful in improving expressive negative symptoms. Our results suggest that we cannot expect to find *the one* intervention for *the* negative symptoms. Rather, some interventions seem to address the motivational deficit better whereas others are better suited to address the expressive deficit.

Our systematic literature review does not claim to be complete. The focus on negative symptoms may be perceived as a narrow one, since we have given scarcely any attention to potentially related topics such as social functioning or positive symptoms. We were also unable to address potential side effects of psychological therapy for negative symptoms. Moreover, our elaboration on the various interventions are based on studies of very different quality and focus, and it might be useful to narrow the focus even more to studies that established an inclusion criterion for negative symptoms. In this regard, it is important to note that the cut-offs for negative symptoms in the various studies that established such a criterion varied. For example, patients in the Klingberg et al. [2011] study had to have at least 1 'moderate' negative symptom on the PANSS; those in the study by Choi et al. [2016] needed at least 2; while the patients in the Velligan et al. [2015] study had to have 2 'clinically significant' negative symptoms that were stable over a 1-month period. Thus, in the future it will also be important to formulate uniform cut-off criteria for negative symptoms.

Since we also considered studies based on hypothesized treatment effects as studies on negative symptoms, we were able to analyze as broad a spectrum of interventions as possible within this narrowly circumscribed field. This helped us taking an initial inventory. The inventory showed that, in addition to the above-mentioned treatment indications, studies are needed, first and foremost, that ensure that the presumed target symptom of the intervention is actually present in the patients.

In summary, the results of our review of the literature clearly show that negative symptoms are principally treatable. We were also able to find evidence of differential efficacy of different approaches for individual negative symptoms. However, given the lack of evidence of efficacy in many instances, it would be premature to make recommendations of any specific individual treatment approaches. Nevertheless, we are cautiously optimistic that it is possible to effectively treat the negative symptoms of schizophrenia and their social consequences. We find it particularly pleasant that most of the interventions presented here should already be part of the treatment repertoire of most psychotherapists, and could thus be put into practice without great difficulty.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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