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Meditation-based mind-body therapies for negative symptoms of schizophrenia: Systematic review of randomized controlled trials and meta-analysis

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ABSTRACT

Meditation-based mind-body therapies (yoga, tai-chi, qi-gong, mindfulness) have been suggested to have a potential therapeutic effect on negative symptoms.

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) examining effectiveness of yoga, tai-chi, qi-gong and mindfulness on negative symptoms of schizophrenia, using different databases and trial registries. The primary outcome was effect of mind-body therapies on negative symptoms and the secondary outcome was effect on positive symptoms.

Fifteen RCTs were included in the meta-analysis ($N = 1081$ patients). Overall, we found a beneficial effect of mind-body interventions on negative symptoms at endpoint compared to treatment-as-usual or non-specific control interventions, but the effect was small and moderate to high heterogeneity was present. A subgroup analysis for different types of therapy revealed a significant effect of mindfulness-based and yoga interventions on negative symptoms, but heterogeneity within the yoga subgroup was high. Our results did not show an increase of positive symptoms ($N = 1051$).

Our results suggest a potential for meditation-based mind-body therapies in the treatment of negative symptoms, in particular for mindfulness based approaches and to a lesser extent yoga. Limitations in the available comparisons do not allow concluding on a specific effect of these interventions. Overall, the currently available evidence remains limited and does not yet allow one to recommend mind-body therapies for the reduction of negative symptoms. However, the present findings justify further research on mind-body therapies for the treatment of negative symptoms.

1. Introduction

Yoga, tai-chi, qi-gong, and mindfulness are different mind-body therapies used to promote general health and to reduce stress. These various forms of meditation practice share commons roots and are suggested to have comparable effects on mind and body, in particular with a small to moderate reduction in multiple negative dimensions of psychological stress (Goyal et al., 2014). In this systematic review we focus on techniques that include meditation as an essential component and do not address other mind-body interventions or psychotherapies. Yoga, tai-chi, qi-gong, and mindfulness include meditation for beginners that consists of basic training of internal concentration by focusing the body and/or breathing, and leads to an altered dynamic of consciousness. Meditation practice is essentially a practice of awareness and all the considered interventions share fundamental meditation exercises such as sited meditation or body-scans (Brown et al., 2015).

Over the last decade researchers have suggested that these group practices could have a therapeutic role for patients suffering from schizophrenia as add-on therapy to antipsychotic treatment (Behere et al., 2011; Helgason and Sarris, 2013; Louise et al., 2018; Vancampfort et al., 2012). Broderick and Vancampfort have provided a series of Cochrane reviews on yoga for schizophrenia (Broderick et al., 2015; Broderick and Vancampfort, 2019). They applied strict inclusion criteria and could only identify a very limited number of small studies that lacked many key outcomes, which precluded concluding on the efficacy of yoga interventions.

In this context the negative symptoms of schizophrenia are a therapeutic target of high interest, as effective treatment remains an unmet therapeutic challenge (Aleman et al., 2017). Several mechanisms of meditation-based mind-body therapies could potentially contribute to an amelioration of negative symptoms. First, empowerment of self-control over symptoms is a common mechanism of these therapies and could support a modification of

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defeatist beliefs associated with negative symptoms (Campellone et al., 2016). Second, meditation has been suggested to stimulate the reward system, which is dysfunctional in patients with negative symptoms, and to improve anhedonia (Kirk and Montague, 2015).

An interesting recent meta-analysis focusing on the broader effects of exercise on negative symptoms has also addressed mind-body exercise (Vogel et al., 2019). The authors included yoga and tai-chi but not mindfulness interventions, thus focusing on the exercise and not the meditation aspect of practice. They found a positive effect of mind-body exercise on negative symptoms, but it is not clear whether this result applies to all meditation-based practice. In addition, they did not perform subgroup analysis to compare different mind-body interventions.

We conducted a systematic review of all randomized clinical trials (RCTs) investigating the effect of meditation-based mind-body therapies as adjunctive treatment to antipsychotic treatment on negative symptoms. Our primary hypothesis was that practice of meditation-based mind-body therapies would lead to a lower negative symptom severity in comparison to treatment-as-usual or to a non-specific control intervention. We did not perform a comparison with specific interventions that have previously been associated with an improvement of negative symptoms (e.g. exercise, social skills training), because we wanted to detect an efficacy signal and not superiority over another form of specific treatment. Our secondary hypothesis was that addition of mind-body therapies would not lead to an increase in positive symptoms.

It has been suggested that longer mind-body interventions have stronger effects, but this question has so far not been addressed in patients with schizophrenia (Carmody and Baer, 2009; Fjorback et al., 2011). Therefore, we planned to explore if negative symptom severity at endpoint is associated with total hours of practice.

2. Methods

2.1. Registration

This work was prepared according to Preferred Reporting items for Systematic reviews and Meta-Analyses (PRISMA-P) guidelines (Moher et al., 2009). On 17th January 2019, the protocol entitled "Mind-body therapies as treatment of negative symptoms of schizophrenia: systematic review of randomized controlled trials and meta-analysis" was published in the International Prospective Register of Systematic Reviews (PROSPERO CRD42019120394); from that date forward it is available from: http://www.crd.york.ac.uk/PROSPERO/.

2.2. Search strategy

The literature was searched with no restriction regarding the date of publication, using Medline, EMBASE, PsychINFO, PsyARTICLES, ScienceDirect and Cochrane Database of Systematic Reviews, from the 2nd to the 30th of March 2019. Additionally, trial registries were also searched for relevant articles: ClinicalTrials.gov and clinicaltrialsregister.eu. The following keywords combinations were used: ("schizo*", psychosis or psychotic), and (yoga, qi-gong, "qi gong", "tai chi", tai-chi, "transcendental meditation", mindfulness, mindfulness-based, meditation, compassion, "loving kindness", or loving-kindness). We used a combination of free-text keywords and MeSH terms to identify a maximum of articles for screening (G.J. Ho et al., 2016). Only English, French and German languages articles were retained. The electronic search was supplemented by examining the reference lists of retrieved articles, and, when available, relevant abstracts for relevant studies. For mindfulness practice, only mindfulness-based programs focusing on mindfulness meditation were considered (e.g. mindfulness-based stress reduction or mindfulness-based cognitive therapies). Interventions that were not based on meditation practice were excluded. In particular, we excluded acceptance-based therapies, which share some elements with mindfulness-based approaches but do not employ formal practice of meditation (Hayes et al., 2006).

2.3. Inclusion criteria and study selection

To be included in the analyses, studies had to fulfill the following criteria: (a) be a rater-blind, controlled randomized trial, (b) report data of patients suffering from schizophrenia or schizoaffective disorder, (c) compare yoga, tai-chi, qi-gong, or mindfulness to a non-specific control intervention or treatment-as-usual, (d) with a duration of intervention of at least 30 min for a total of 8 h of practice over a minimum of 3 weeks; these criteria were selected because effects on negative symptoms need time to develop and these characteristics can be found in standard mindfulness-based program format which have the most empirical support for its efficacy among meditation-based interventions (Carmody and Baer, 2009); (e) report results in English, German or French language, (f) report results on negative symptoms as means and standard deviations or statistical values. Concerning the comparison conditions non-specific control interventions could include any form of intervention not previously associated with an improvement of negative symptoms (e.g. leisure therapy, occupational therapy). We excluded reviews, pilot/single dose studies, case reports, and case series (Fig. 1). Cross-over RCTs were excluded as carry-over effects of considered mind-body therapies are unknown.

2.4. Outcomes and data extraction

Our primary outcome was the effect of adjunctive mind-body therapies on negative symptoms, as assessed with the negative subscale of Positive and Negative Syndrome Scale (PANSS-N) (Kay et al., 1987), the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989) or another scale reporting negative symptoms. Secondary outcome was the effect of adjunctive mind-body therapy on positive symptoms as assessed by the positive subscale of the Positive and Negative Syndrome Scale (PANSS-P), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) or another scale reporting positive symptoms. Review authors (M.S. and S.K.) independently screened for eligibility titles, trials protocol and abstracts of papers identified in the electronic searches (Fig. 1). The reviewers then examined full-text of retained articles. When they disagreed a common full-text discussion of the paper was done.

For the final set of RCTs we conducted quality assessment of methodology following criteria described in Cochrane handbook for systematic reviews of interventions to assess risk of bias (Higgins et al., 2011). In addition to assessment of the different types of bias, we aggregated these categorizations into a summary bias score as described in the legend to Table 2. Discrepancies were resolved upon discussion between the two raters.

After qualitative analysis, one reviewer (M.S.) performed data extraction for meta-analysis, and one author checked data for accuracy (S.K.). In case of lacking data, the principal authors of studies were contacted by email. In case of trials evaluating multiple active interventions, only the mind-body therapy arm and the control arm were considered. For one study of interest endpoint scores for the primary outcome was not available (Visceglia and Lewis, 2011), but we were able to impute the PANSS negative endpoint scores based on the Ikai et al. (2014) study reporting baseline, change and endpoint scores for our primary and secondary outcome (Abrams et al., 2005). Additionally, for Ho et al. (2012), we imputed the SANS total score from the SANS domains scores, using the correlation matrix from a previously published dataset (Bischof et al., 2016).

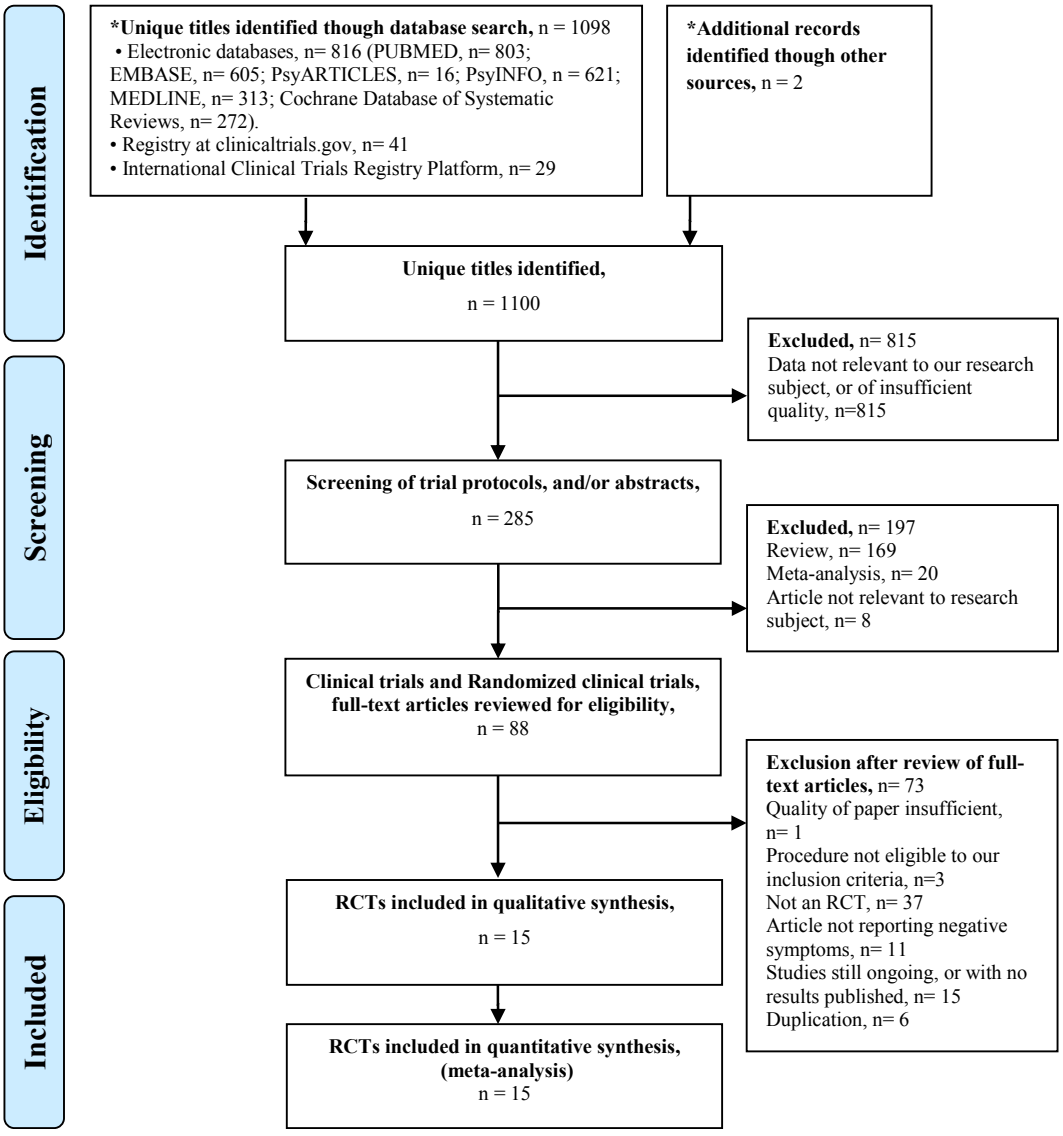

Fig. 1. Systematic review PRISMA flowchart.

2.5. Statistical analysis

Analyses were performed using Review Manager (RevMan) Version 5.3, a Cochrane collaboration software. Meta-regression was conducted with Stata software Version 15.0. For primary and secondary outcome standard mean differences were used, because different scales were reported across studies. Extracted scores were endpoint scores of considered interventions. Analysis of follow-up scores was not possible, because reporting was too heterogeneous. Since the protocols of the retained studies were heterogeneous, random effects models were applied for all analyses. Heterogeneity between studies was estimated by using I^2 statistic combined to Chi^2 p value.

For exploration of heterogeneity a subgroup analysis focusing on the type of intervention was performed. Finally, we conducted a meta-regression in order to explore residual heterogeneity by examining the effect of intervention duration and baseline negative symptoms severity on our main outcomes. The between-study variance ($\tau 2$) was estimated using the method of moments and the assumption of homogeneity in effects was tested using the Q statistic with a k-1 degree of freedom.

3. Results

3.1. Search results

The systematic review searches yielded 1100 unique references. On the basis of their title, 815 articles were excluded for reasons described in flow-chart (Fig. 1). Screening of abstract and trial protocol led to 197 exclusions, leaving 88 articles for full-text article review for eligibility. One study was excluded for insufficient duration of intervention (20 min per sessions, for a total of 4 h of practice) (Ikai et al., 2017). Two studies with a light aerobic exercise group as a control group were excluded (Duraiswamy et al., 2007; Manjunath et al., 2013), because aerobic exercise has previously been associated with an improvement of negative symptoms and can thus be considered a specific intervention for negative symptoms (Dauwan et al., 2016). One study compared a community-based integrated intervention including tai-chi and social skills training to treatment as usual (Kang et al., 2016). We excluded this study, because social skills training is one of the few evidence-based interventions for negative symptoms and the combination treatment thus precludes the identification of specific tai-chi

Table 1
Characteristics of included studies.

Study	Type and duration of trial	Key inclusion criteria/outcomes	Inclusions (male, gender %) Mean age (mean ± SD)		Baseline negative symptom scores[a]	Baseline positive symptom scores[b]	Dose of antipsychotics CPZE[c] mg/day (mean ± SD)	Procedure
Yoga studies								
1-Behere et al., 2011 (India)	8 week, single-blind randomized controlled study. Per-protocol analysis.	Outpatients with a diagnosis of schizophrenia (DSM-IV). Stabilized on antipsychotic for 6 weeks or longer. Age 18 to 60 years. PANSS scale.	Yoga group	18 (66%) 31.3 ± 9.3	17.8 ± 4.9	15.1 ± 11.7	335.0 ± 205.3	Yoga consisted in breathing practice, sitting, supine, and prone posture, along with relaxation techniques. Participants practiced for one month, with additional homework for 2 months. Total of 45 h of practice over 3 months. The waitlist group did not receive any add-on intervention.
			Waitlist group	15 (68%) 33.6 ± 9.9	14.3 ± 3.7	14.7 ± 6.3	340.0 ± 172.4	
2-Visceglia et al., 2011 (United States of America)	8 week, single-blind randomized controlled study. Per-protocol analysis.	Inpatients with an Axis-I diagnosis of schizophrenia. Age 20 to 58 years. PANSS scale.	Yoga group	10 (60%) 37.40 ± 13.73	19.1 ± 8.1	21.6 ± 6	n.a.[d]	Eight-week yoga classes with pranayama (breathing exercises), asana (yoga postures), and yoga nidra (deep relaxation). Total of 12 h of practice over 8 weeks. The waitlist group did not receive any add-on intervention.
			Waitlist group	8 (75%) 48.13 ± 11.24	19.4 ± 4.5	20.2 ± 7.3	n.a	
3-Varambally et al., 2012 (India)	4 week, single-blind randomized controlled study. Per-protocol analysis	Outpatients with a diagnosis of schizophrenia (DSM-IV). On stabilized antipsychotic for 6 weeks or longer. Patients were of 18 to 60 years-old. PANSS scale.	Yoga group	47 (60.9%) 32.8 ± 10.0	18.1 ± 5.7	15.9 ± 5.3	n.a.	The patients learnt yogasana for one month (25 sessions), and then practiced at home over the three months. Total of 60 h of practice over 4 months. The waitlist group did not receive any add-on intervention.
			Waitlist group	36 (73%) 33.6 ± 9.5	15.3 ± 5.4	14.7 ± 6.2	n.a.	
4-Jayaram et al., 2013 (India)	4 week, single-blind randomized controlled study. Per-protocol analysis.	Patients with a diagnosis of schizophrenia (DSM-IV), with stable dose of antipsychotics for 6 weeks. Exclusion of substance disorders. Age 18 to 55 years. SANS and SAPS scales.	Yoga group	15 (n.a.) n.a	20.8 ± 5.3	16.9 ± 4.6	400 ± 200	The Yoga module consisted of loosening exercises, relaxation techniques, breathing practices, sitting, supine and prone posture. Total of 15 h of practice over 4 weeks. The waitlist group did not receive any add-on intervention.
			Waitlist group	28 (n.a.) n.a.	17.8 ± 3.1	16.7 ± 2.5	300.5 ± 250	
5-Ikai et al., 2013 (Japan)	8 week, single-blind randomized controlled study. Intention-to-treat analysis	Outpatients with a diagnosis of schizophrenia or related psychotic disorder (F20-F29, ICD-10). Exclusion of patients with substance use disorders. Patients had stable medication for 8 weeks. Age 18 years and older. PANSS scale.	Yoga group	16 (64%) 54.8 ± 9.0	20.3 ± 3.4	23 ± 6.8	512.2 ± 393.2	Eight-week sessions of yoga therapy (warm-ups, loosening-up exercises, asana, deep relaxation and breathing exercises). Total of 8 h of practice over 8 weeks. The waitlist group benefit of a regular daycare consisting of social skills training, and psycho-education.
			Waitlist group	16 (67%) 51.5 ± 15.1	15.5 ± 5.3	18.1 ± 4.8	701.3 ± 360.1	
6-Ikai et al., 2014 (Japan)	8 week, single-blind randomized controlled study. Intention-to-treat analysis.	Outpatients with a diagnosis of schizophrenia or related psychotic disorder (F20-F29, ICD-10). Exclusion of patients with substance use disorders. Patients had stable medication for 8 weeks. Age 18 years and older. PANSS scale.	Yoga group	16 (64%) 53.5 ± 9.9	21.1 ± 5.3	21.1 ± 4.4	659.3 ± 386.2	Eight-week sessions of hatha-yoga therapy (yoga stretches in coordination with breathing, asana, deep relaxation, and breathing exercises). Total of 8 h of practice over 8 weeks. The waitlist group with regular daycare consisting of social skills and walking.
			Waitlist group	17 (68%) 48.2 ± 12.3	15.6 ± 5.1	16.9 ± 5.1	733.5 ± 432.5	
7-Isuru et al., 2015 (Sri Lanka)	3 week, single-blind randomized controlled study. Per-protocol analysis.	Inpatients with a diagnosis of schizophrenia (ICD-10). PANSS scale.	Yoga group	33 (n.a.) 38.7 ± 9.5	18 ± 5.5	19 ± 4	n.a.	Exposure to yoga, dance, drama, and music therapy (training with breathing control, emotions, behavior, body posture, self-confidence, social interactions, communication). Total of 48 h of practice over 3 weeks. The non-specific control leisure activities and occupational therapy.
			Control group	40 (n.a.) 41.9 ± 9.8	16 ± 5	15 ± 4.3	n.a.	
8-Paikkatt et al., 2015 (India)	4 week, single-blind randomized controlled study. Per-protocol analysis.	Outpatients with a diagnosis of schizophrenia (F20, ICD-10). Exclusion of patients with substance use disorders. On stabilized antipsychotic dose for a minimum of 2 weeks. Age 20 to 50 years. PANSS scale.	Yoga group	15 (100%) n.a.	23.5 ± 4.4	24.5 ± 5.0	n.a.	Yoga therapy consisted of different postures: standing, sitting, lying posture postures, chakra with mantra, breathing exercises. Total of 30 h of practice over 4 weeks. The control group did not receive any add-on intervention.
			Control group	15 (100%) n.a.	23.1 ± 4.9	22.3 ± 4.5	n.a.	

9-Bhatia et al., 2017 (India)	26 week, single-blind randomized controlled study. Intention-to-treat analysis	Outpatients with a diagnosis of schizophrenia (DSM-IV). Clinically stable patients with stable treatments. Exclusion with substance use disorder. Patients with prior experience of yoga were excluded. Age 18 years or older. SANS and SAPS scales.	Yoga group	104 (59.6%) 34.7 ± 9.5	14.8 ± 5.9	15.3 ± 6.1	n.a.	The yoga practice consisted of postures, breathing and weekly nasal cleansing, introduced to participants with a one-month supervised practice. Total of 21 h of supervised practice followed by 5 months home practice. The waitlist group did not receive any add-on intervention.
			Waitlist group	92 (61.9%) 35.7 ± 10.0	14.3 ± 3.8	14.5 ± 3.1	n.a.	
10-Lin et al., 2015 (China)	12 week, single-blind randomized controlled study. Intention-to-treat analysis	Female outpatients diagnosed with schizophrenia spectrum (F20-F29; DSM-IV). Patients on stable medication. Age 18 to 60 years. PANSS scale.	Yoga group	23 (0%) 23.8 ± 6.8	10.8 ± 4.2	10.2 ± 3.7	339 ± 263	Hatha yoga consisted of breathing control, body postures, and relaxation. Total of 36 h of practice over 3 months. The waitlist group did not receive any add-on intervention.
			Waitlist group	18 (0%) 25.3 ± 8.1	11.2 ± 4.1	9.9 ± 3.8	260 ± 211	
Tai-chi studies								
11-Ho et al., 2012 (China)	6 week, single-blind randomized controlled study. Intention-to-treat analysis	Inpatients with chronic schizophrenia (DSM-IV-TR). No prior experience of tai-chi. Follow-up after intervention. Age 18 to 65 years. SANS scale.	Tai-chi group	15 (60%) 51.87 ± 10.85	11.5 ± 2.7	11.8 ± 2.8	391.0 ± 472.2	The tai-chi class was based on the Wu-style Cheng-form tai-chi Chuan with an emphasis on movement rhythm, and movement coordination. It consists of 22 simple movement forms. Total of 15 h of practice over 6 weeks. The waitlist group received their standard residential care which included a 30-minute daily morning stretching routine for both the tai-chi and control participants.
			Waitlist control	15 (20%) 53.47 ± 8.63	n.a.	n.a.	365.1 ± 221.9	
12-R.T. Ho et al., 2016 (China)	12 week, no-blind randomized controlled study. Per-protocol analysis.	Outpatients with a diagnosis of schizophrenia (DSM-IV TR). Patients were stabilized on antipsychotic with no substance use disorders. Total PANSS scores ≤ 60. No formal training of tai-chi prior to enrollment. Age 18 to 65. PANSS scale.	Tai-chi group	51 (61%) 52.4 ± 9.6	12.4 ± 5.6	6.4 ± 2.9	n.a.	The tai-chi intervention was based on the Wu-style Cheng-form tai-chi Chuan, comprising 22 simple movements. Total of 30 h of practice over 12 weeks. The waitlist group did not receive any add-on intervention, as both group received
			Waitlist group	49 (50%) 54.7 ± 8.0	12.2 ± 5.9	6.8 ± 4.3	n.a.	
Mindfulness studies								
13-Lopez-Navarro et al., 2015 (Spain)	26 week, single-blind randomized controlled study. Intention-to-treat analysis	Outpatients with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder (DSM-IV). On stabilized antipsychotic medications for 4 weeks. No prior experience of mindfulness or yoga. Patients were of 18 to 65 years-old. PANSS scale.	MBI[e] group	22 (77.3%) 38.77 ± 8.93	21.7 ± 6.3	17.9 ± 6.6	n.a.	The mindfulness-based intervention group consisted of body-awareness, guided meditation, cognitive treatment, reflective group discussion. Home practice was encouraged between mindfulness sessions with audio tapes. Total of 26 h of practice over 6 months. The waitlist group did not receive any add-on intervention. Both groups received 'Integrated Rehabilitation Treatment' consisting of medication, cognitive-behavior therapy, and illness management.
			Treatment-as-usual	21 (86%) 38.73 ± 7.46	20 ± 6.2	15.9 ± 6.2	n.a.	
14-Chien et al., 2017 (China)	26 week, single-blind randomized controlled study. Intention-to-treat analysis.	Outpatients with a diagnosis of schizophrenia (DSM-IV). Patients were stabilized on antipsychotic with no substance use disorders. Patient had not practice mindfulness and/or other therapies in the past 2 years. Age 18 to 64. PANSS scale.	MBPEG[f] group	114 (63%) 25.1 ± 6.8	19.9 ± 7.3	20.1 ± 6.8	n.a.	The mindfulness program was based on Kabat-Zinn's mindfulness-based stress reduction program modified for psychotic patients in the Chinese cultural context. Total of 48 h of practice over 24 weeks. The treatment-as-usual group did not receive any add-on intervention.
			Treatment-as-usual	12 (65%) 26.0 ± 8.5	20.1 ± 9.1	20.1 ± 8.0	n.a.	
15-Lee, 2019 (Taiwan)	8 week, single-blind randomized controlled study. Follow-up period. Intention-to-treat design.	In and outpatients being diagnosed on the schizophrenia Spectrum. Exclusion of patients exhibiting psychotic symptoms. Patients were of 18 to 64 years-old. SANS and PANSS scales.	MBI group	20 (n.a.) 54.4 ± 6.3	21.6 ± 5.6	14.9 ± 2.9	n.a.	Mindfulness-based program was adapted for schizophrenia patient with a program based on a self-awareness, self-regulation, and self-transcendence model of mindfulness. Total of 12 h of practice on 8 weeks. The treatment-as-usual group received occupational rehabilitation twice a week (nutrition counseling, nursing care, health education group, walking sessions, mild doses of antipsychotic drugs).
			Treatment-as-usual	30 (n.a.) 51.1 ± 6.3	21.9 ± 11.5	13.7 ± 4.3	n.a.	

[a] SANS baseline scores were converted to PANSS negative scores to allow comparison between studies (van Erp et al., 2014).
[b] SAPS baseline scores were converted to PANSS positive scores to allow comparison between studies (van Erp et al., 2014).
[c] CPZE: chlorpromazine.
[d] n.a.: not available.
[e] MBI: mindfulness-based intervention group.
[f] MBPEG: mindfulness-based psychoeducation group.

effects (Turner et al., 2018). Fifteen studies were included in the qualitative synthesis, 10 yoga, 2 tai-chi, and 3 mindfulness studies.

3.2. Qualitative description of included studies

The 15 studies retained included patients who met DSM-IV or DSM-IV-TR criteria (Table 1) for schizophrenia or schizoaffective disorder ($n = 549$ for the intervention subjects, and $n = 532$ for the control subjects). One study included patients suffering from other psychotic disorders representing <0.1% of total inclusions (Lopez-Navarro et al., 2015). The population consisted mainly of outpatients with the exception of three inpatient studies (Ho et al., 2012; Isuru et al., 2015; Lin et al., 2015). Only 5 studies precisely reported baseline types of antipsychotics and chlorpromazine equivalents (249 patients, mean dose of 454.1 mg/day).

All studies included stabilized patients. Twelve studies required a stable antipsychotic medication at inclusion. Eight studies specified a minimum of 2 to 8 weeks of clinical stability and unchanged antipsychotic medication. Only 4 studies reported depressive symptoms at inclusion and during intervention (R.T. Ho et al., 2016; Lee, 2019; Lin et al., 2015; Visceglia and Lewis, 2011). Six studies excluded patients having a prior experience of proposed meditation practice ($n = 837$).

Three yoga studies had an emphasis on homework practice after a one month instructor-led intervention (Behere et al., 2011; Bhatia et al., 2017; Varambally et al., 2012). In contrast, the three mindfulness-based studies encouraged only a small amount of homework between each instructor-led session (Chien et al., 2017; Lee, 2019; Lopez-Navarro et al., 2015). For the 15 included studies in our quantitative analysis mean duration of intervention was of 14.5 weeks, with an estimated 29.5 h of total therapy.

Four studies had a treatment-as-usual control group (Chien et al., 2017; Lee, 2019; Lopez-Navarro et al., 2015; Paikkatt et al., 2015) and one study employed a non-specific control intervention of no specified duration consisting of leisure activities and occupational (Isuru et al., 2015). All other studies had waiting list as control group with treatment as usual during the study period (Table 1).

3.3. Effect of mind-body therapies on negative symptoms

There were 1081 patients included in this analysis of 10 yoga, 2 tai-chi, and 3 on mindfulness interventions. All but three studies used the PANSS negative subscale. Three studies used the SANS (Bhatia et al., 2017; Ho et al., 2012; Jayaram et al., 2013).

Overall, we found a statistically significant beneficial effect of mind-body therapies on negative symptoms in comparison with treatment-as-usual and non-specific control interventions, albeit with a small effect size and in presence of high heterogeneity ($I^2 = 62\%$ (SMD, −0.36; 95% CI, −0.58 to −0.15; $p = 0.0008$) (Fig. 2).

Subgroup analysis yielded a non-significant effect for the 2 tai-chi studies (SMD, −0.16; 95% CI, −0.50 to +0.19; $p = 0.38$) (Fig. 2). For the 10 yoga studies, a significant beneficial effect of mind-body therapies on negative symptoms score was found (SMD, −0.39; 95% CI, −0.72 to −0.06; $p = 0.02$) but in presence of high heterogeneity ($I^2 = 73\%$). For the 3 mindfulness studies we found a significant beneficial effect on negative symptoms with a medium effect size (SMD, −0.45; 95% CI, −0.67 to −0.23; $p < 0.0001$) in absence of heterogeneity ($I^2 = 0\%$). Heterogeneity between subgroups was absent ($I^2 = 0.3\%$). Equal dispersion of included studies for each intervention on correspondent funnel plot for this analysis was not in favor of asymmetry (Fig. 3).

3.4. Meta-regressions focusing on negative symptoms

In order to explore a possible association between hours of practice and negative symptom severity at endpoint, we performed a meta-regression with total hours of practice as independent variable. This meta-regression was limited to the yoga study subgroup, since it was the only subgroup with heterogeneity ($I^2 = 73\%$). Total hours of practice did not predict severity of negative symptoms at endpoint (SMD, −0.01; 95% CI, −0.04 to +0.04; $p = 0.9$) (Supplementary Fig. 1).

Furthermore, we conducted another meta-regression in order to explore a possible association between the effect observed on negative symptom at endpoint and baseline negative symptom severity. All scores were converted to PANSS-N scores (van Erp et al., 2014). Baseline severity did not predict the changes of negative symptoms at endpoint (SMD, −0.02; 95% CI, −0.1 to +0.06; $p = 0.5$).

3.5. Effect of mind-body therapies on positive and general symptoms

All included studies except Ho et al. (2012) reported positive symptoms. Overall results did not show a significant change in the severity of positive symptoms (SMD, −0.19; 95% CI, −0.39 to +0.001; $p = 0.05$), in presence of a moderate overall heterogeneity ($I^2 = 54\%$). There was moderate heterogeneity between subgroups ($I^2 = 47.6\%$).

We conducted a subgroup analysis for the different interventions (Fig. 4). This analysis revealed that only the yoga subgroup showed a significant advantage regarding positive symptoms, but with a small effect-size (SMD, −0.27; 95% CI, −0.53 to −0.01; $p = 0.04$) and moderate heterogeneity ($I^2 = 56\%$). The correspondent funnel plot identified the Paikkatt et al. (2015) study as an outlier. A sensitivity analysis revealed that with exclusion of this study, heterogeneity was reduced ($I^2 = 32\%$) and changes in positive symptoms were no longer significant (SMD, −0.16 95% CI, −0.36 to +0.05; $p = 0.14$). Tai-chi and mindfulness practice did not lead to significant change in positive symptoms. The correspondent funnel plot was not in favor of asymmetry (Supplementary Fig. 2).

General psychopathology symptoms endpoint scores were available for 7 studies using the PANSS scale. We did not find a significant effect of meditation-based mind-body therapies on general symptoms (SMD, −0.38; 95% CI, −0.82 to +0.06; $p = 0.09$), but heterogeneity was high ($I^2 = 75\%$) (Supplementary Fig. 3). We conducted a sensitivity analysis excluding the Isuru et al. (2015) study as an outlier, which resulted in a significant beneficial effect of yoga on general symptoms (SMD, −0.63; 95% CI, −0.92 to −0.33; $p < 0.0001$) in absence of heterogeneity ($I^2 = 0\%$).

3.6. Exploratory analysis of the association between negative and positive symptoms

In treatment studies it is an important question whether an effect on negative symptoms is secondary to an effect on positive symptoms. It was not possible to conduct a meta-regression, because neither study-level covariances nor individual-level data were available. Therefore, we conducted a descriptive analysis of the association between treatment effects on negative and positive symptoms across studies (Fig. 5). The scatterplot clearly suggests an association and the corresponding Spearman correlation coefficient was high ($r_s = 0.69$). Significance testing was not possible and this approach has to be considered purely descriptive.

3.7. Sensitivity analysis including only studies with a low risk of bias

We conducted a sensitivity analysis including only the studies with a low risk of bias (Table 2). Two studies on yoga and two

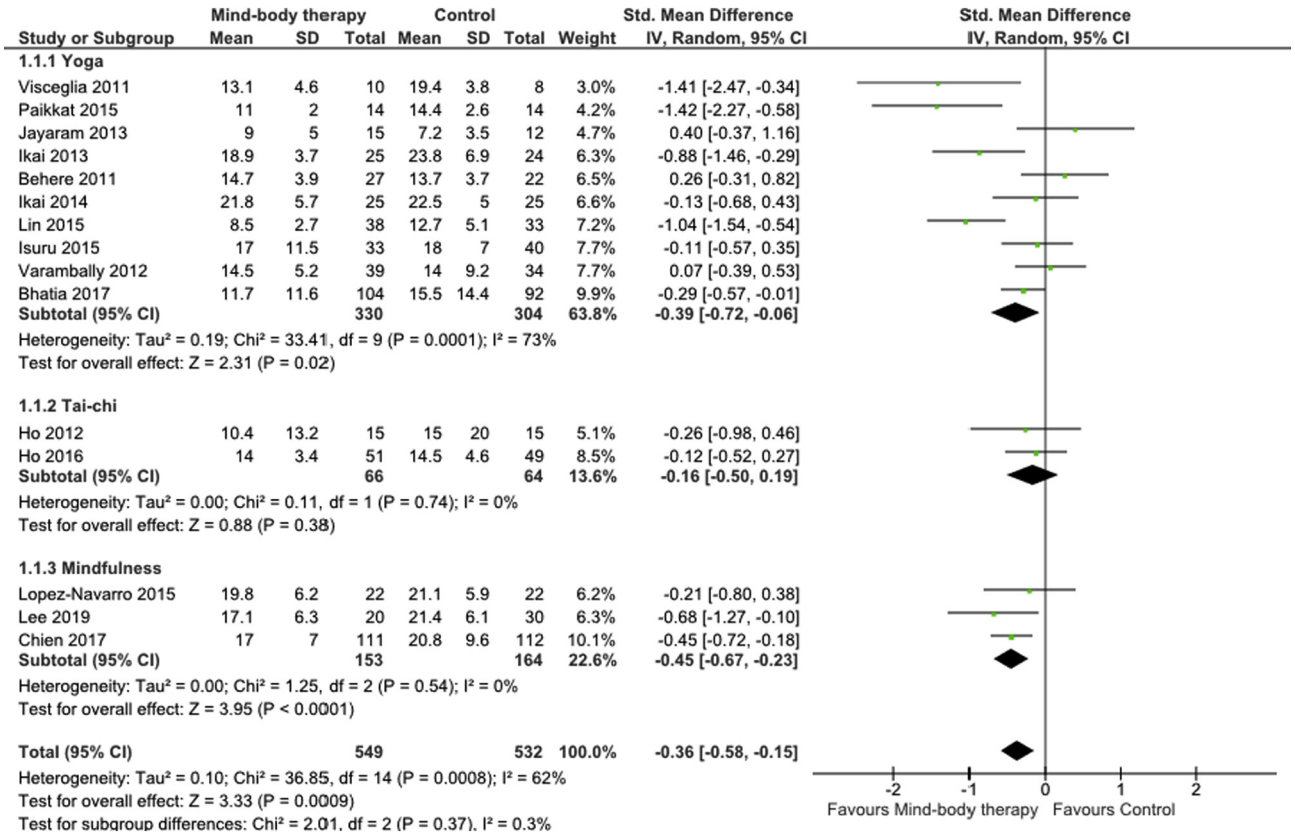

Fig. 2. Forest plot for negative symptoms.

studies on mindfulness were retained (Chien et al., 2017; Ikai et al., 2014; Lin et al., 2015; Lopez-Navarro et al., 2015). For negative symptom an overall beneficial effect was present (SMD, −0.47; 95% CI, −0.83 to −0.12; $p = 0.009$) in presence of a moderate heterogeneity ($I^2 = 58\%$). Subgroup analysis showed a beneficial effect for mindfulness, but not for yoga interventions. For positive symptoms, we observed a beneficial overall effect (SMD, −0.33; 95% CI, −0.57 to −0.08; $p = 0.009$). Subgroup analysis showed a beneficial effect on positive symptoms for yoga, but not for mindfulness. A similar pattern was found for PANSS general symptoms with a beneficial overall effect (SMD, −0.51; 95% CI, −0.88 to −0.14; $p = 0.007$) and a beneficial subgroup effect for yoga, but not for mindfulness.

4. Discussion

4.1. Effects of mind-body therapies on negative symptoms

To our knowledge this is the first meta-analysis to evaluate the potential therapeutic effect of mind-body therapies on negative symptoms including all meditation-based practices. Overall, we found a small beneficial effect of mind-body interventions on negative symptoms compared to treatment-as-usual or non-specific control interventions in the presence of high heterogeneity. Subgroup analysis allowed to partially account for heterogeneity and showed positive effects of mindfulness and yoga therapies on negative symptoms, while this was not the case for tai-chi studies.

One recent meta-analysis has included yoga and tai-chi studies in an investigation of exercise effects on negative symptoms (Vogel et al., 2019). The observed effect size was somewhat higher than in our study, but heterogeneity for mind-body exercise including tai-chi and yoga was high. As the authors took a broader approach including other forms of exercise, they did not conduct an analysis for yoga and tai-chi subgroups to explore this heterogeneity within the mind-body exercise subgroup. One difference to our study is the more liberal inclusion criteria without the definition of a minimum duration and intensity of treatment.

Importantly, in our study mindfulness-based therapies showed the highest effect size in the absence of heterogeneity, while this approach was not included in the Vogel et al. (2019) study. The effect of mindfulness therapies was consistent across the three included studies. It is important to note that these three mindfulness studies were more recent and had generally less bias than most of the included studies on yoga and tai-chi. Another important characteristic of the mindfulness studies is the central role of

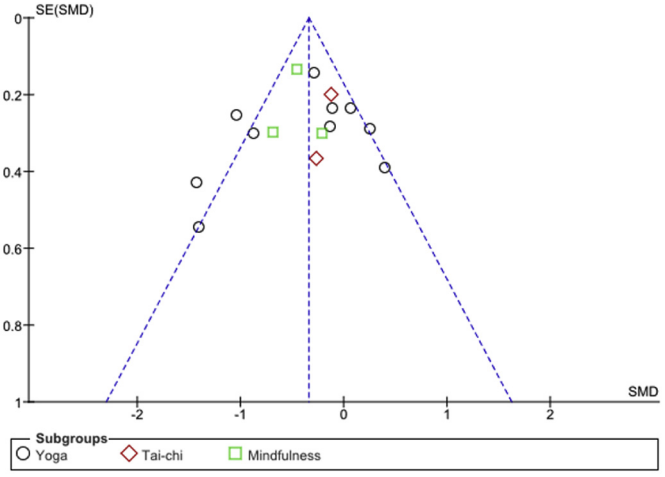

Fig. 3. Funnel plot for negative symptoms.

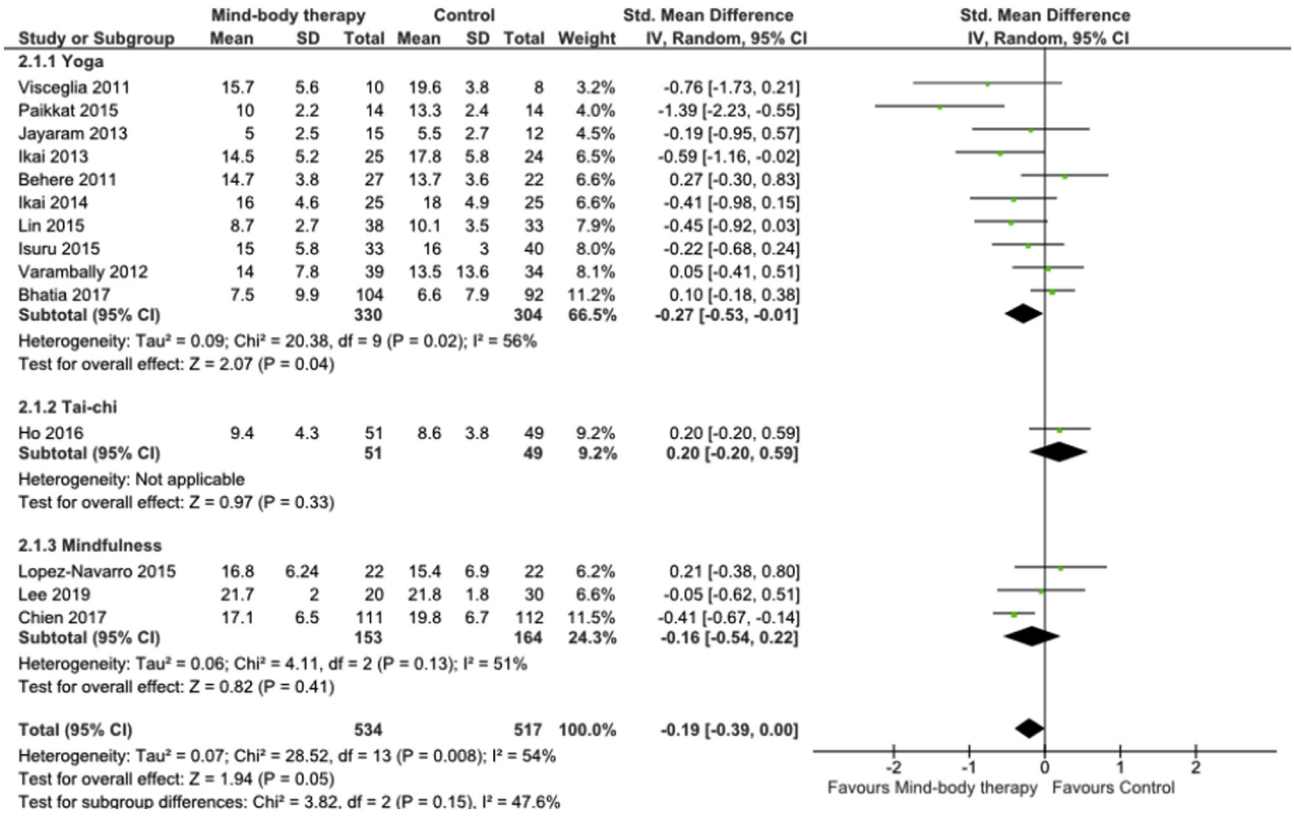

Fig. 4. Forest plot for positive symptoms.

instructor led group practice although some homework was required. As only three studies were available and heterogeneity was absent, we did not analyze the impact of treatment duration in this subgroup.

In contrast, within the yoga subgroup considerable heterogeneity remained. Treatment duration was not associated with treatment effect and therefore, other factors contributing to heterogeneity must be considered.

4.2. Effects of mind-body therapies on positive and general symptoms

Our results revealed that mind-body therapies do not worsen positive symptoms. The small improvement of positive symptoms in yoga studies disappeared after exclusion of an outlier and should thus interpreted with caution. Nevertheless, the absence of negative effects on positive symptoms is an important finding, because concerns about meditation-based practices for patients suffering from psychotic illness have been raised (Chadwick, 2014). An adaptation of these therapies to patients with schizophrenia is certainly necessary, but it seems more relevant for assuring treatment adherence than for avoiding risks.

In addition, our results suggest that yoga might have a beneficial effect on general psychopathology. Overall, it seems that yoga might not lead to a specific improvement of negative symptoms, but rather has a more general effect, possibly related to increased well-being.

4.3. Clinical relevance of the effects on negative symptoms

Regarding the clinical relevance of the observed effects of mindfulness and yoga, the quantity and the quality of the effects need to be considered. The effect size is in the small to moderate range, which might be of questionable clinical relevance. Nevertheless, it is important to note that negative symptoms are often chronic and difficult to treat. Thus, even small improvements in symptoms might be relevant to the patient. Other interventions for negative symptoms do not show greater effects, for example add-on treatment with antidepressants (Helfer et al., 2016) or social skills training (Turner et al., 2018).

Importantly, none of the included studies specifically required patients to have predominant or primary negative symptoms. Primary negative symptoms are defined by excluding secondary causes of negative symptoms, such as positive symptoms, depression or medication side-effect. The definition of predominant negative symptoms would require patients to have a minimum severity of negative symptoms and more negative than positive symptoms. Our exploratory analysis did suggest an association between improvement in negative and positive symptoms across studies. Although this observation has to be interpreted with caution due to methodological limitations, it is conceivable that the effect of mind-body therapies on negative symptoms is secondary to an effect on positive symptoms. In addition to positive symptoms a major cause of secondary negative symptoms is depression. Only four studies screened depressive symptoms of included population, these studies were also the only ones to assess depressive symptoms during intervention. Therefore an improvement of negative symptoms secondary to improvement of depressive symptoms cannot be excluded.

Overall, the observed results suggest a potential for clinical relevance, but negative symptoms will have to be better characterized at inclusion and during the course of the study. Differentiation of primary and secondary negative symptoms should be performed during the screening and the intervention with

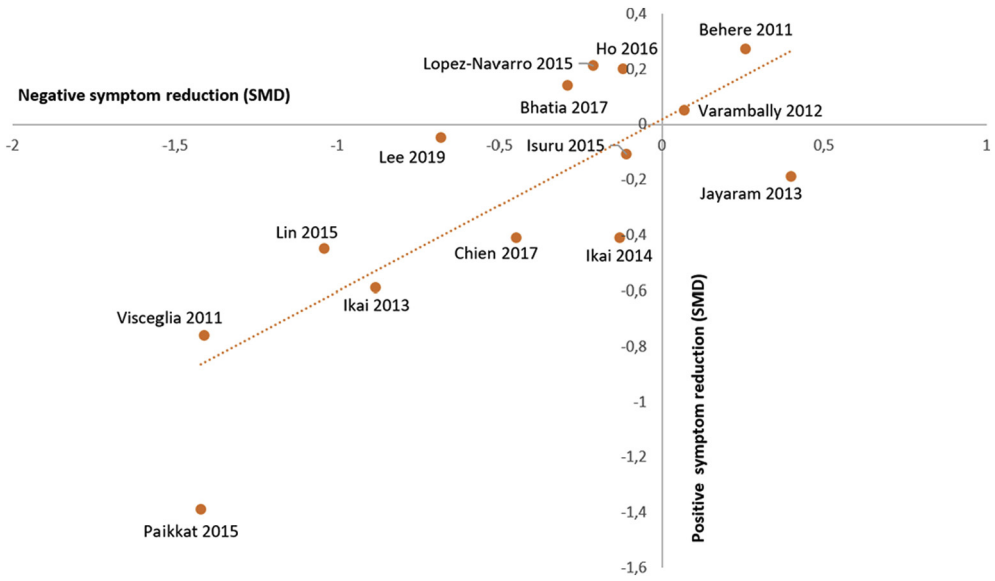

Fig. 5. Comparison of SMDs for negative and positive symptoms. Line shows Spearman's rho ($r_s = 0.69$).

Table 2
Cochrane Collaboration risk of bias assessment for included RCTs.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Bias score
1-Behere et al., 2011	Low risk	High risk	Unclear	Low risk	High risk	Low risk	No funding statement	3/6
2-Visceglia and Lewis, 2011	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk		4/6
3-Varambally et al., 2012	Low risk	Low risk	Unclear	Low risk	High risk	Unclear	No funding statement	3/6
4-Ho et al., 2012	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear		3/6
5-Ikai et al., 2013	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear		4/6
6-Jayaram et al., 2013	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	No funding statement	0/6
7-Ikai et al., 2014	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		5/6
8-Lopez-Navarro et al., 2015	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		6/6
9-Lin et al., 2015	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		5/6
10-Paikkatt et al., 2015	Unclear	Unclear	Unclear	Unclear	Unclear	High risk		0/6
11-Isuru et al., 2015	Unclear	Unclear	Unclear	Low risk	Low risk	High risk		2/6
12-G.J. Ho et al., 2016; R.T. Ho et al., 2016	Low risk	Unclear	High risk	High risk	Unclear	Unclear		1/6
13-Chien et al., 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk		6/6
14-Bhatia et al., 2017	Low risk	Low risk	Low risk	High risk	High risk	Low risk		4/6
15-Lee et al., 2019	Low risk	Low risk	Unclear	High risk	Unclear	Low risk		3/6

Criteria for judging risk of bias in the 'Risk of bias' assessment tool followed the Cochrane handbook recommendations:
Low risk: the investigators describe a random component for the considered risk.
Unclear: insufficient information to permit judgment of 'low risk' or 'high risk'.
High risk: the investigators describe a non-random component.
Authors' assessment of the overall risk of bias. A summary score was calculated with 0 for each category with high or unclear risk and 1 for each category with low risk. Based on the summary score the overall risk was defined as follows:
Low risk: bias score ≥ 5.
Moderate risk: $3 \leq$ bias score ≤ 4.
High risk: bias score < 3.

appropriated scales. Although current recommendations for RCTs targeting negative symptoms have mostly been developed for pharmacologic agents, they could be of equal interest for psychotherapeutic interventions (Marder and Kirkpatrick, 2014).

4.4. Limitations

The main limitation of our meta-analysis studies concerns the nature of obtained data. Our conclusions are from a pool of studies with mostly limited sample size, short-term and per-protocol analysis. Our risk of bias assessment reveals that four studies had a high risk of bias, while generally many biases remained unclear. However, the beneficial effects on negative symptoms of meditation-based mind-body therapies and mindfulness in particular remained significant in a sensitivity analysis only including the four studies with low risk of bias.

In the present meta-analysis we were not able to include any study adequately controlling for non-specific effects such as therapist attention or group setting. We excluded studies that employed an intervention previously associated with a beneficial effect on negative symptoms as the only control arm (Duraiswamy et al., 2007; Kang et al., 2016; Manjunath et al., 2013). Thus, we cannot conclude on a specific effect of mind-body interventions. As a next step it would be important to evaluate efficacy in comparison to an adequately matched non-specific control condition. Subsequently, comparison of mind-body interventions with other interventions targeting negative symptoms would be of interest.

Overall, in future trials it will be important to describe the interventions in more detail. One important point participating to subgroup heterogeneity is the instructor experience, which is known to influence the study outcomes (Ruijgrok-Lupton et al., 2018). Only one study reported concerning instructor experience (Chien et al., 2017). The participant's previous experience of mind-body therapy can also have an important impact and the information was lacking for most studies. We would suggest that future studies exclude participants who have one year or more of experience with mind-body practice, as it seems unlikely that an intervention based on the same principles can have an incremental effect on their symptoms.

An important issue is the potential impact of the cultural context. In our sample, only two studies were conducted in Western countries (Table 1). In addition, several studies from China, Korea and India could not be included, because they were not available in English. This pattern clearly shows that studies in mind-body therapies were first conducted in Asian countries, in particular for yoga therapy. This is important, because the foundations of these interventions are much more anchored in the Asian local cultural contexts than in Western countries. It is therefore an open issue whether the present results translate to Western countries, but several studies on mindfulness for patients with schizophrenia are currently on-going in Europe and should provide answers to these questions.

5. Conclusions

Our results suggest a potential for meditation-based mind-body therapies in the treatment of negative symptoms, in particular for mindfulness based approaches and to a lesser extent yoga. Across all treatment approaches we did not find any evidence for worsening of positive symptoms. It is important to note that none of the studies did primarily target negative symptoms, nor did they correspond to current recommendations for RCTs targeting negative symptoms. Therefore, it is not possible to conclude on the effects on primary or predominant negative symptoms. In addition, only three studies were available for the mindfulness-based approaches showing the highest effect size. The current evidence does not yet allow recommending mind-body therapies for the treatment of negative symptoms. However, the present findings clearly justify further research on mind-body therapies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.030.

Contributors

MS, OS and SK designed the study and wrote the protocol. MS and SK conducted the literature searches and data collection. MS analyzed the data. MS wrote the first draft of the manuscript. MS, OS, and SK reviewed the final version of the manuscript.

Declaration of competing interest

Stefan Kaiser has received royalties for cognitive test and training software from Schuhfried and advisory board honoraria from Recordati and Lundbeck on an institutional account for research and teaching. Othman Sentissi has received advisory board honoraria from Otsuka, Lilly, Lundbeck, Sandoz, and Janssen on an institutional account for research and teaching. Michel Sabe declares no conflict of interest.

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