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Treatment of negative symptoms: Where do we stand, and where do we go?

André Aleman [a,*], Tania M. Lincoln [b], Richard Bruggeman [c], Ingrid Melle [d], Johan Arends [e], Celso Arango [f], Henderikus Knegtering [a,g]

[a] University of Groningen, University Medical Center Groningen, Department of Neuroscience, Groningen, The Netherlands
[b] Clinical Psychology and Psychotherapy, Department of Psychology, University of Hamburg, Germany
[c] University of Groningen, University Medical Center Groningen and Rob Giel Research Center, Department of Psychiatry, Groningen, The Netherlands
[d] NORMENT and K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, 0424 Oslo, Norway
[e] GGZ Drenthe Mental Health Center, Department of Psychotic Disorders, Assen, The Netherlands
[f] Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain
[g] GGZ Lentis Mental Health Center, Department of Psychotic Disorders, Groningen, The Netherlands

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ABSTRACT

Negative symptoms, e.g. social withdrawal, reduced initiative, anhedonia and affective flattening, are notoriously difficult to treat. In this review, we take stock of recent research into treatment of negative symptoms by summarizing psychosocial as well as pharmacological and other biological treatment strategies. Major psychosocial approaches concern social skills training, cognitive behavior therapy for psychosis, cognitive remediation and family intervention. Some positive findings have been reported, with the most robust improvements observed for social skills training. Although cognitive behavior therapy shows significant effects for negative symptoms as a secondary outcome measure, there is a lack of data to allow for definite conclusions of its effectiveness for patients with predominant negative symptoms. With regard to pharmacological interventions, antipsychotics have been shown to improve negative symptoms, but this seems to be limited to secondary negative symptoms in acute patients. It has also been suggested that antipsychotics may aggravate negative symptoms. Recent studies have investigated glutamatergic compounds, e.g. glycine receptor inhibitors and drugs that target the NMDA receptor or metabotropic glutamate 2/3 (mGlu2/3) receptor, but no consistent evidence of improvement of negative symptoms was found. Finally, some small studies have suggested improvement of negative symptoms after non-invasive electromagnetic neurostimulation, but this has only been partly replicated and it is still unclear whether these are robust improvements. We address methodological issues, in particular the heterogeneity of negative symptoms and treatment response, and suggest avenues for future research. There is a need for more detailed studies that focus on different dimensions of negative symptoms.

1. Introduction

Negative symptoms in schizophrenia are characterized by marked reductions in goal-directed behavior, which can include speech and social behavior. The lack of activity is reflected in reduced initiative, social withdrawal, anhedonia, affective flattening and poverty of speech, amongst others. One or more negative symptoms are present in approximately 60% of outpatients (Bobes et al., 2010), whereas persistent negative symptoms may be present in 30% of patients with schizophrenia (Kirkpatrick et al., 2006). It should be noted that several issues regarding the definition and boundaries of negative symptoms remain to be further elucidated, and such research will certainly also inform treatment research and practice. For example, the distinction between primary and secondary negative symptoms receives continuing attention in the literature (see also this special issue, articles by Mucci et al.,2017 and Kirschner et al., 2017). A relationship with cognitive dysfunction has been established (Dominguez et al. 2009; Aleman et al., 1999), but the effect sizes are small to moderate. In addition, a relationship with abnormalities of dopaminergic reward systems has been established (Radua et al., 2015).

It is easy to understand that such reductions in activity hamper functioning in daily life, and indeed negative symptoms are associated with poor psychosocial functioning (Lysaker and Davis, 2004). A recent study in 7678 patients found negative symptoms to be associated with increased likelihood of hospital admission, longer duration of admission, and increased likelihood of readmission following discharge (Patel

* Corresponding author at: Department of Neuroscience, University Medical Center Groningen, Antonius Deusinglaan 2, Groningen, The Netherlands.
E-mail address: a.aleman@umcg.nl (A. Aleman).

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et al., 2015). Negative symptoms are therefore an important target for treatment. However, no treatments have as yet emerged to be reliably and robustly effective, as evidenced from large clinical trials. Thus, negative symptoms seem to be more difficult to address than the positive symptoms that define psychotic disorders. This is not to say that no improvements can be achieved at the individual patient level. In this review, we provide an overview of recent research into treatment approaches for negative symptoms by summarizing psychosocial as well as pharmacological and other biological treatment strategies. The goal of this paper was to briefly summarize evidence on current treatments and to highlight novel approaches. To this aim, databases (PubMed and Web of Science) were searched in July 2015 using relevant keywords (e.g., combinations of schizophrenia and negative symptoms with cognitive behav*, psychosocial, antipsychot*, glutamat*, transcranial) to identify papers on psychosocial, pharmacological and neurostimulation trials of schizophrenia.

2. Psychosocial interventions for negative symptoms

Negative symptoms are generally targeted along with other outcome domains in psychological interventions for schizophrenia spectrum disorders. These interventions can be broadly classified into skill-focused interventions, individual psychological interventions, and family interventions.

The most intensively studied skill focused intervention is social skill training (SST). SST targets participants' social functioning by training verbal and nonverbal communication alongside perception and responses to social cues in order to improve their ability to perform in social situations (e.g. Bellack et al., 1997). In a review of outcome studies for negative symptoms 11 controlled trials on SST were identified (Elis et al., 2013). Two of these compared SST to treatment as usual (TAU) and the remaining studies compared SST to an active control group. Five studies found SST to be associated with a change in negative symptoms at post-treatment which was maintained at six-month follow-up in two studies. A recent meta-analysis also found SST to be superior to other interventions ($k = 9$; Turner et al., 2014). Nevertheless both groups of researchers stress the need for further and methodologically improved studies.

Another skill focused intervention is cognitive remediation that targets basic cognitive processes. Although cognitive impairment has often been subsumed under negative symptoms in the past, researchers now widely agree that it is conceptually distinct from negative symptoms (Kirkpatrick et al., 2006). This might explain why, on their own, these interventions have not been found to improve negative symptoms (Elis et al., 2013). However, cognitive remediation combined with components that address social skills or problem solving have produced more promising effects, e.g. Cognitive Enhancement Training (Eak et al., 2013) or the Integrated Psychological Therapy (Roder et al., 2006).

Family interventions differ in characteristics and methods but generally involve providing support to the family and enlisting families as therapeutic agents. They are usually part of a treatment package used in conjunction with routine drug treatment and outpatient clinical management (Dixon and Lehman, 1995). Elements most frequently used are psycho-education, communication training, behavioral problem solving, and crisis management. The majority of studies on family intervention alone or in combination with other interventions demonstrate an improvement in negative symptoms (e.g. Dyck et al., 2000; Elis et al., 2013; Giron et al., 2010, Calvo et al., 2014).

The most widely studied individual psychological intervention is cognitive behavioral therapy for psychosis (CBTp) that aims to support patients in achieving personally meaningful goals by promoting awareness of the links between thoughts, behaviors, and feelings to help implement changes in symptoms and functioning by modifying unhelpful thoughts and self-defeating behavior (NICE, 2009). CBTp was originally developed for positive symptoms, which is why samples in outcome studies were mostly preselected for positive rather than negative symptom severity and negative symptoms are seldom a primary outcome. Meta-analyses of negative symptoms as a secondary outcome nevertheless indicate a significant effect of CBTp for negative symptoms (Velthorst et al., 2015; Wykes et al., 2008). However, the moderate effect size found for the first generation of CBT (Wykes et al., 2008) do not appear to be generalizable to more recent studies (Velthorst et al., 2015). Furthermore, only few studies have focused primarily on negative symptoms. Klingberg et al. (2011) investigated the effect of specifically designed CBT for negative symptoms compared to cognitive remediation in a randomized controlled trial (RCT) including 198 patients diagnosed with schizophrenia and related disorders with at least one negative symptom of moderate severity. The intervention included developing a shared formulation followed by treatment modules addressing different negative symptoms over a mean number of 17.6 sessions. Although both groups improved from pre- to post assessment, negative symptoms did not improve more in the CBTp than in the cognitive remediation condition. Another recent adaptation of CBTp builds on empirical studies that have found negative symptoms to be associated with dysfunctional beliefs (e.g. “Finding new friends is not worth the energy I would have to invest.”) (Grant and Beck, 2010), a reduced sense of self-efficacy (Bentall et al., 2010), low expectations of success (Beck et al., 2009), and low self-esteem (Lincoln et al., 2011). Grant et al. (2012) used a cognitive approach to challenge these beliefs in a RCT including 60 patients with psychotic disorders and prominent negative symptoms. They found a significant improvement in functioning at the end of an 18-month period including 50.5 treatment sessions on average. Improvements were found for apathy and avolition but not for anhedonia, flat affect and alogia. In support of the treatment rationale, a subsequent small uncontrolled pilot trial (Staring et al., 2013) that used the same approach over a shorter period of six-months found the pre- to post effect size for negative symptoms to be partially mediated by a change in dysfunctional beliefs. To conclude, CBT may be effective in reducing negative symptoms, but further controlled trials with negative symptoms as a primary outcome are needed.

Direct comparisons of the different interventions in regard to negative symptoms seem to favor SST over other interventions so far (Turner et al., 2014). However, further replications and standardization of measurements and designs are warranted before drawing definite conclusions (Elis et al., 2013). Some evidence suggests that treatment packages that combine several different interventions (e.g. family psychoeducation and skill training) achieve better outcomes than stand-alone interventions (Hogarty et al., 1986). In accord with this finding the recently developed “Motivation and Enhancement Therapy” (MOVE, Velligan et al., 2015) combined environmental support, CBT, skills training, and other components in an attempt to address all domains of negative symptoms. Their preliminary results in an RCT including 51 patients with clinically meaningful negative symptoms suggest that MOVE improves negative symptoms. However, the group differences were not significant until 9 months of treatment and not for all negative symptom scales.

3. Antipsychotics

Only few studies have been designed to evaluate the effects of antipsychotics on negative symptoms as a primary outcome measure (Möller and Czobor, 2015). Most studies into the efficacy of antipsychotics concern acutely ill patients, versus placebo, or compare antipsychotic to each other. These studies often last for 6 to 12 weeks. Improvement of negative symptoms occurs during improvement of positive symptoms in these acutely ill patients. In these studies it is difficult to disentangle whether an effect on negative symptoms concerns primary or secondary negative symptoms (Arango et al., 2004). Primary negative symptoms are those that are not a consequence of other symptoms or medication. When the improvement of initiative and goal-directed behavior is due to a reduction of anxiety, depression, delusions

or hallucinations, the treatment can be considered to have targeted secondary negative symptoms.

In studies of antipsychotics versus placebo, aimed primarily to reduce positive symptoms, second generation antipsychotics such as amisulpride, clozapine, olanzapine and risperidone showed a small to medium effect size in reducing negative symptoms in patients with acute psychosis (Leucht et al., 2009). A recent meta-analysis reported a medium sized effect size of d = 0.54 for second generation antipsychotics (Fusar-Poli et al., 2015). Although clozapine is thought to be one of the most effective antipsychotics, studies fail to clearly support its effects on primary negative symptoms (Buchanan et al., 1998). It has been concluded that most studied antipsychotics (amisulpride, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone) are superior to placebo in the treatment of negative symptoms in acutely ill patients, and that amisulpride and ziprasidone may show the largest effect sizes (Möller and Czobor, 2015). However, because these improvements typically occur in the early stages of treatment and go together with the improvement of psychotic symptoms, antipsychotics are not viewed as being very effective in the treatment of primary negative symptoms. Nonetheless, a number of studies have reported improvement of persistent negative symptoms following treatment with olanzapine versus amisulpride (compared to placebo; Lecrubier et al., 2006), risperidone versus haloperidol (Möller et al., 1995) and olanzapine or asenapine (Buchanan et al., 2012). Supporting an independent effect on chronic negative symptoms, the study by Möller et al. (1995), based on data from 523 chronic patients with schizophrenia, path analysis showed that the greater mean change of negative symptoms with risperidone compared to haloperidol could not be fully explained by correlations with effects on positive and extrapyramidal symptoms.

Antipsychotics have also been suggested to contribute to the development of apathy, flat affect and other negative symptoms (Awad, 2010). A study with a single dose of risperidone or haloperidol in healthy volunteers confirmed this possibility: the antipsychotics increased negative symptoms, especially avolition/apathy (Artaloytia et al., 2006). On the other hand, a recent study suggested that antipsychotics may not strongly affect amotivation in patients with schizophrenia (Fervaha et al., 2015). This study analyzed data from 250 patients who were receiving antipsychotic mono-therapy for at least 6 months and were followed prospectively. They were receiving one of five antipsychotic medications (olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone). There was no association between dosage or level of sedation and negative symptoms. Moreover, one hundred and twenty-one individuals were identified as antipsychotic-free at baseline, and showed no change in motivation after 6 months of antipsychotic treatment.

4. Targeting the glutamate/GABA system

Accumulating evidence suggests a dysregulation of central nervous system (CNS) glutamatergic activity as contributing to the pathophysiology of schizophrenia (Kinon et al., 2015). Hyperactive and dysregulated cortical pyramidal neurons in key brain regions, such as the thalamus, prefrontal cortex, and limbic system may be a result. A hypofunction of the *N*-Methyl-D-Aspartate Acid (NMDA) receptor may be underlying changes in the glutamate system (Arango et al., 2013; Veerman et al., 2016). The hypofunction of the NMDA receptor may be secondary to reduced inhibitory influences of the GABA system causing a hyperstimulation of glutamatergic pyramidal neurons, possibly leading to neurotoxic effects. Consideration of putative mechanisms generated interest in investigational drugs such as NMDA-receptor co-agonists, that may compensate for hypofunction of the NMDA-receptor. On the other hand, emerging evidence suggests that GABA may be increased, rather than reduced, in un-medicated schizophrenia patients (Kegeles et al., 2012), and subjects at ultra-high risk (de la Fuente-Sandoval et al., 2015). This may suggest that illness phase-specific pharmacotherapy should be explored (Krystal and Anticevic, 2015).

Alternatively, metabotropic glutamate 2/3 (mGlu2/3) receptor agonists are thought to be able to normalize a putatively heightened activity of cortical pyramidal neurons and may offer a non-dopamine D2 receptor antagonist-dependent mechanism to treat schizophrenia. The few trials that have been conducted regarding negative symptoms did not find improvements over and above placebo, however (Adams et al., 2014; Stauffer et al., 2013; Kinon et al., 2011). Interestingly, a recent exploratory study suggested that there might be subgroups in which such agents could be effective in reducing schizophrenia symptoms (Kinon et al., 2015). In this study, data were analyzed for five placebo-controlled trials in which patients with schizophrenia received the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil. The authors report that only patients early-in-disease or previously treated with CNS drugs with predominantly D2 receptor antagonist activity, in the absence of 5-HT2A receptor antagonism, exhibited significantly greater improvement relative to those receiving placebo, when treated with pomaglumetad. This effect was specific for 40 mg twice daily, and was not observed at 80 mg. This may signal a complex, may be U shaped, dose effect relation in desired treatment effects when targeting the glutamate system. Notably, this study reported total Positive and Negative Syndrome Scale (PANSS) scores only, and did not report separately on negative symptoms (Kay et al., 1987). As it would be of interest to know specific changes for negative symptoms, we recommend future studies to include relevant measures.

4.1. Glycine, D-serine, D-cycloserine, sarcosine and bitopertin

The activity the NMDA-receptor is modulated in several ways, including through glycine receptors. Endogenous glycine, sarcosine (=D-methylglycine), *N*-acetyl-cysteine (NAC), D-serine and D-cycloserine have been studied as add-on medication to antipsychotics. In a meta-analysis (n = 343) of 18 randomized placebo controlled studies with glutamatergic drugs, Tuominen et al. (2005) found a mean reduction of 4 points on the subscale for negative symptoms of the PANSS.

In a smaller meta-analysis, regarding glycine addition to clozapine, no effects on negative symptoms were identified (Evins et al., 2000). Yet another meta-analysis (Singh and Singh, 2011) led the authors to conclude that D-serine, NAC and sarcosine as adjuncts to non-clozapine antipsychotics may be beneficial in the treatment of negative and total symptoms of chronic schizophrenia. Unfortunately there are many contradictory findings. It should be noted, though, that by far the largest trial with glycine and D-cycloserine was negative, i.e. no significant effect of the glutamatergic agents (Buchanan et al., 2007). In the case of D-cycloserine, one reason for contradictory findings may be that it may even increase negative symptoms through competition with endogenous glycine. While glycine has been reported to improve positive and total symptoms as an adjuvant to non-clozapine antipsychotics, it seems to worsen them when added to clozapine (Singh and Singh, 2011). It has been suggested that there may be an optimal level of activity through the NMDA receptor, explaining sometimes contradictory effects of addition strategies to clozapine, in comparison to other antipsychotics (Veerman et al., 2014). It can be hypothesized that clozapine also targets the glutamate system and therefore add-on strategies additionally targeting the glutamate system through the NMDA receptor may surpass optimal levels of glutamatergic stimulation.

A recent treatment strategy involves attempting to increase the glycine levels in the brain through a selective glycine re-uptake inhibitor such as bitopertin. However, in a series of short (4 weeks) and long-term (12 months) Phase II/III studies with bitopertin, added to non-clozapine antipsychotics, no clinically meaningful improvements on negative symptoms were detected (Bugarski-Kirola et al., 2014; Goff, 2014).

4.2. Lamotrigine, topiramate, valproate, carbamazepine

Lamotrigine, topiramate, valproate and carbamazepine are registered as anticonvulsants and are also in use as mood stabilizers. Their activity is partly linked to modulating effects on the glutamate system. Lamotrigine caused a reduction of ketamine induced negative symptoms in healthy volunteers (Anand et al., 2000). Although a meta-analysis of lamotrigine added to clozapine did suggest some effects in improving negative symptoms (Tiihonen et al., 2009), a recent meta-analysis did not find evidence of a significant effect on negative symptoms (Veerman et al., 2014). The latter included 6 studies of lamotrigine add-on therapy to clozapine and 4 studies of topiramate addition to clozapine. Moreover, a limited number of studies on the addition to other antipsychotics of topiramate, valproate and carbamazepine did not suggest an effect on negative symptoms (see review by Jiawan et al., 2010).

4.3. Memantine

Memantine is an uncompetitive NMDA receptor open-channel blocker, registered for the treatment of Alzheimer's disease. It is thought to hold promise for its potential clinical effectiveness as add-on therapy to on-going treatment with antipsychotics, including clozapine (Paraschakis, 2014; Veerman et al., 2014). In a double-blind, placebo-controlled study adding 20 mg memantine or placebo for 12 weeks to treatment with clozapine, appeared to improve negative and positive symptoms as evaluated by using the Brief Psychiatric Rating Scale, with large effect sizes (De Lucena et al., 2009). In a retrospective case control study (26 patients), memantine addition was found to improve negative symptoms in 11 patients (John et al., 2014). In a 12 week, double blind cross-over study of 20 mg memantine added to the treatment of clozapine-treated refractory patients with schizophrenia, memantine addition significantly improved verbal and visual memory and negative symptoms (Veerman et al., 2016). All studies reported a good tolerability of memantine addition.

4.4. Minocycline

Minocycline, a broad-spectrum tetracycline antibiotic, may have neuroprotective effects in different neurological conditions. Minocycline may also have effects against glutamate neurotoxicity or modulate the NMDA or AMPA receptors. Several case reports suggested that minocycline in addition to second generation antipsychotics including clozapine may improve positive and negative symptoms (Kelly et al., 2011). In several randomized double-blind placebo-controlled clinical trials an improvement was found on negative symptoms in patients with schizophrenia (Liu et al., 2014; Kelly et al., 2015). This was confirmed in a recent meta-analysis (Oya et al., 2014), even though the total sample size was still small (330 patients, 4 studies).

4.5. Antidepressants

Antidepressants are frequently prescribed in patients with schizophrenia, especially to improve depressive symptoms or, less frequently, to improve negative symptoms. These symptom dimensions are not always readily separable. Meta-analyses or systematic reviews do not give a congruent picture on possible effects of antidepressants to improve negative symptoms when given in addition to antipsychotics. Singh et al. (2010) included 23 trials from 22 publications (N = 819) in a systematic review and meta-analysis. The antidepressants included were selective serotonin reuptake inhibitors, mirtazapine, reboxetine, mianserin, trazodone and ritanserin; trials on other antidepressants were at that moment (until august 2009) not available. The overall standardized mean difference was moderate (−0.48) in favor of antidepressants. Subgroup analysis revealed significant responses for fluoxetine, trazodone and ritanserin. In a review of the addition of antidepressants to antipsychotics for negative as well as depressive symptoms it was recently concluded that mirtazapine and mianserin showed "somewhat consistent" efficacy on negative symptoms and both seemed to enhance neurocognition (Terevnikov et al., 2015). This is in part in line with a meta-analysis focusing on the add-on treatment with mirtazapine; it was concluded that mirtazapine was effective in improving negative symptoms (Vidal et al., 2013). According to a recent review, several trials, mostly with modern antidepressants such as the SSRIs, selective dual action antidepressants and alpha-2 receptor blocking antidepressants, have tested add-on approaches in relatively small samples showing some evidence of efficacy of combing antipsychotics with antidepressants (Möller and Czobor, 2015). A key issue is whether patients with depressive symptoms (or concurrent diagnosis of major depressive disorder) were included in the analysis or not. When they are excluded, antidepressants may not improve the negative symptoms (Arango et al., 2000).

5. Other pharmacological add-on to antipsychotics interventions

Several other mechanisms have been studied as add on to antipsychotics with the aim of improving negative symptoms in patients with schizophrenia. The MAO-B inhibitors selegiline and rasagiline have shown some promise of improving negative symptoms (Buchanan et al., 2015). Also the addition of oestrogens and selective estrogen receptor modulators (SERMs) may hold some promise, although side effects may limit its use (Heringa et al., 2015). The literature suggests that stimulants (DA agonists) such as methylphenidate, amphetamine, and modafinil or armodafinil may improve negative symptoms without worsening of positive symptoms in patients who are stable and treated with effective antipsychotic medications, but the studies lack the rigorous designs required in order to draw firm conclusions (Lindenmayer et al., 2013). Several studies are underway using alpha-7 nicotinic receptor (partial) agonists like bradanicline or encenicline in addition to antipsychotics, targeting cognitive and negative symptoms (Deutsch et al., 2013). Recent results do not support the effectiveness of bradanicline for negative symptoms (Walling et al., 2016). It is to early to draw definite conclusions on the effectiveness or tolerability of these approaches.

6. Oxytocin

Intranasal administration of oxytocin has recently been studied as a therapy for improving symptoms of schizophrenia, based on findings in animals that oxytocin can promote social behavior (Teng et al., 2013). Seven trials in patients with schizophrenia (reported before 2016) were recently reviewed and the authors concluded that six trials found improvement in negative symptoms was following use of oxytocin, but possible long-term effects remain unclear (Feifel et al., 2016). A trial that was published later, failed to observe a significant effect of oxytocin on negative symptoms (Dagani et al., 2016). Clearly, more and larger trials are needed.

7. Neurostimulation

Noninvasive neurostimulation using electromagnetic fields is increasingly being studied in psychiatric disorders (cf. Aleman, 2013) and has been applied in patients with schizophrenia to alleviate positive and negative symptoms (Dougall et al., 2015). The two forms of neurostimulation that have been studied in several trials are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). In rTMS, strong magnetic pulses (up to 1.5 T) are applied over the scalp in order to affect cortical excitability in the underlying tissue (up to 2–3 cm. deep).

In contrast to rTMS, tDCS involves weak electric fields, with currents of 1–2 mA. Even though the precise mechanism of action of rTMS and tDCS awaits full elucidation, a number of differences are known (Priori et al., 2009). For example, tDCS does not induce neuronal firing by

supra-threshold neuronal membrane depolarization, as happens in rTMS, but rather modulates spontaneous neuronal network activity through a tDCS polarity-dependent shift (polarization) of resting membrane potential. Anodal tDCS stimulation generally enhances cortical activity and excitability, whereas cathodal tDCS stimulation may reduce excitability (Paulus, 2011).

7.1. rTMS

Three meta-analyses have been conducted on studies reporting effects of prefrontal rTMS on negative symptoms in schizophrenia (Freitas et al., 2009; Dlabac-de Lange et al., 2010; Shi et al., 2014). They included 8, 9 and 16 studies respectively, and the latter two reported statistically significant mean effect sizes of stronger improvement after rTMS as compared to sham stimulation (in which a placebo coil is used, or the coil is rotated by 90 degrees so as not to allow magnetic pulses to enter the brain). The mean effect sizes were of small-to-moderate magnitude, ranging from 0.27 to 0.53. Two studies of frontal cortex stimulation, published after these meta-analyses, show mixed results. Dlabac-de Lange et al. (2015) reported an improvement of negative symptoms (as measured with the SANS) after 3 weeks (five days a week) of 10 Hz stimulation over the dorsolateral PFC (bilaterally; twice daily). The study included a total of 32 patients. The most recent, and largest trial, however failed to find a stronger improvement of negative symptoms in the rTMS condition as compared to sham (Wobrock et al., 2015). This trail included 76 patients in the experimental group and 81 patients in the sham-control group. They were treated with 10-Hz rTMS (either real or sham) applied 5 days per week for 3 weeks to the left DLPFC (added to the ongoing treatment). Thus, rTMS at these parameters may not improve negative symptoms in a majority of patients. However, the latter study only included the PANSS, which may be less sensitive to change than the Scale for the Assessment of Negative Symptoms (SANS) (Lane et al., 2005). Studies are now underway that investigate the effects of theta-burst rTMS over the prefrontal cortex, which has been suggested to induce stronger neural changes and has a shorter administration duration (Chung et al., 2015). One preliminary study using this frequency has already been published, albeit over the cerebellar vermis (Demirtas-Tatlidede et al., 2010). These authors studied 8 treatment-refractory patients with schizophrenia (no sham control group), and reported an improvement of negative symptoms.

7.2. tDCS

Only a few studies have investigated the effects of tDCS on negative symptoms so far. The first study to report on this (Brunelin et al., 2012) was designed to test tDCS as an experimental treatment for auditory hallucinations in schizophrenia and included only 15 patients in each group (real vs. placebo). Thus, negative symptoms were not a primary outcome measure. Nonetheless, the authors observed a reduction of hallucination severity and a concurrent improvement of negative symptoms. They ascribe this effect to the location of the electrodes: The anode was placed over the left dorsolateral prefrontal cortex and the cathode over the left temporo-parietal cortex. However, a small follow-up study in 24 patients who were randomized to real (either unilateral or bilateral) or sham stimulation did not find improvement of either positive nor negative symptoms (Fitzgerald et al., 2014). Smith et al. (2015) reported the results of a randomized double-blind, sham-controlled study of the effects of 5 sessions of tDCS on cognitive performance, with PANSS scores as secondary outcome measure. They included data of 30 patients and found an improvement of memory performance, but not of PANSS scores. In conclusion, the studies evaluating tDCS for negative symptoms (albeit in two out of three as secondary outcome) in schizophrenia are inconclusive and lack sufficient statistical power. Thus, at this moment there is no evidence for tDCS as a treatment for negative symptoms, but larger well-powered studies are necessary to reach stronger conclusions.

8. General discussion

The search for effective treatments of negative symptoms has not yielded therapies that robustly improve such symptoms. Novel approaches, including tailored cognitive-behavioral therapy, glutamatergic compounds and noninvasive neurostimulation deserve further development and further investigation, but there are no well-replicated large trials with negative symptoms as primary outcome measure that have shown evidence for enduring clinically significant improvements up until now. Though it is promising that negative symptoms have been found to improve in psychosocial and pharmacological interventions for psychosis that were not aimed primarily at negative symptoms, it is also concerning that RCTs that focus primarily on negative symptoms using intensive treatments in preselected samples have not produced strong effects. This indicates that the effects from other samples cannot be readily generalized to low-functioning patients with moderate to severe negative symptoms and that more effective interventions await to be developed for this group. This illustrates the heterogeneity in treatment response. Moreover, it should be acknowledged that changes in negative symptoms may be difficult to detect in a clinical setting. This is not only due to measurement issues (better trained clinicians/researchers with observational data of patient behavior will achieve more reliable measurement), but also to the fact that once brain functioning is ameliorated, it may take time for this to translate to behavioral change. In this regard, it is of interest that studies with rTMS have noted that the effects of treatment were stronger when measured weeks after treatment than immediately after treatment (Li et al., 2016).

An additional problem concerns the heterogeneity of negative symptoms before treatment, an issue that has been neglected in treatment studies. For example, it remains difficult to disentangle whether primary or secondary negative symptoms were treated. Better assessment of negative symptoms using recently developed instruments may be helpful in this regard (e.g., Kring et al., 2013; Dollfus et al., 2016). In a similar vein, only few interventions have been sufficiently tailored to the central dimensions of negative symptoms, expressive deficits and social amotivation (e.g. Liemburg et al., 2013) and effects could possibly be improved by interventions that are tailored towards these aspects (cf. Foussias et al., 2015). A first promising step in this direction was attempted in an uncontrolled pilot study targeting deficits in anticipatory pleasure and anhedonia (Favrod et al., 2010). Another approach that could improve outcome in negative symptoms is to further elucidate the mechanisms that are involved in negative symptom formation and maintenance and to intervene at this level, including the direct manipulation of regional brain excitability through neurostimulation. The research on the relevant role of dysfunctional beliefs by Beck et al. (2009) and interventions challenging negative beliefs (Grant et al., 2012) can also be subsumed along this line. Relatedly, there is room for improvement within the framework of cognitive-behavioral interventions for psychosis by placing more emphasis on the exploration of negative symptoms, which are in some cases a response to adverse experiences and developing a shared understanding of negative symptoms that conceptualize them as part of a chain of preceding and following internal and external factors (e.g. beliefs, problems in concentration, medication, positive symptoms, lack of stimulation, chronic stressors, health problems, lack of movement or sleep, substance abuse etc.). Tailoring treatment to the individually relevant factors that are identified in this process is likely to lead to better treatment results. Similarly, different parameters of neurostimulation should be explored (e.g. theta-burst rTMS) and novel pharmacological compounds deserve further investigation as does the interaction of agents such as D-cycloserine with psychosocial approaches (including cognitive training, e.g. Cain et al., 2014). These types of approaches are currently being further developed and it will be exciting to witness their progress over the coming decades.

Conflict of interest

AA has received speaker honoraria from Lundbeck; CA has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Forum, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Schering Plough and Takeda. HK has received speaker honoraria from Lundbeck, Janssen and Lilly. He received research grants from Lilly, Astra Zeneca, ZonMW, Stichting Roos.

Contributors

AA, TL, and HK conceptualized the structure of the manuscript and managed the literature searches. AA, TL, and HK wrote the first draft of the manuscript, with input from CA, RB, IM, and JA. All authors contributed to and have approved the final manuscript.

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