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Review

Effects of intranasal oxytocin on symptoms of schizophrenia: A multivariate Bayesian meta-analysis

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ABSTRACT

Schizophrenia is a heterogeneous disorder in which psychiatric symptoms are classified into two general subgroups—positive and negative symptoms. Current antipsychotic drugs are effective for treating positive symptoms, whereas negative symptoms are less responsive. Since the neuropeptide oxytocin (OT) has been shown to mediate social behavior in animals and humans, it has been used as an experimental therapeutic for treating schizophrenia and in particular negative symptoms which includes social deficits. Through eight randomized controlled trials (RCTs) and three meta-analyses, evidence for an effect of intranasal OT (IN-OT) has been inconsistent. We therefore conducted an updated meta-analysis that offers several advantages when compared to those done previously: (1) We used a multivariate analysis which allows for comparisons between symptoms and accounts for correlations between symptoms; (2) We controlled for baseline scores; (3) We used a fully Bayesian framework that allows for assessment of evidence in favor of the null hypothesis using Bayes factors; and (4) We addressed inconsistencies in the primary studies and previous meta-analyses. Eight RCTs ($n = 238$) were included in the present study and we found that oxytocin did not improve any aspect of symptomology in schizophrenic patients and there was moderate evidence in favor of the null (no effect of oxytocin) for negative symptoms. Multivariate comparisons between symptom types revealed that oxytocin was not especially beneficial for treating negative symptoms. The effect size estimates were not moderated, publication bias was absent, and our estimates were robust to sensitivity analyses. These results suggest that IN-OT is not an effective therapeutic for schizophrenia.

Contents

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1. Introduction

Schizophrenia is a neurological disorder with a lifetime prevalence of 4.0 per 1000 persons (Saha et al., 2005). A heterogeneous disorder (Buchanan and Carpenter, 1994), psychiatric symptoms are often classified into two general subgroups—positive and negative symptoms(Andreasen et al., 1994). Positive symptoms are characteristics that are gained such as delusions and/or hallucinations, whereas negative symptoms are comprised of characteristics that diminish overtime including motivation, social functioning, and the ability to express emotions (Millan et al., 2014). Many factors have been implicated in the etiology and expression of schizophrenia, which include environmental perturbations (Khandaker et al., 2013; Qeoffrey Davies et al., 2003), genetic risk factors (Sullivan et al., 2003; O'Donovan et al., 2008), and certain brain abnormalities (Lawrie and Abukmeil, 1998). Increased dopaminergic transmission in the mesolimbic pathway (Winton-Brown et al., 2014), reduced gray matter volume, and cortical thickness (Padmanabhan et al., 2015) are thought to be associated with positive symptoms. Irregular glutamate levels in several brain regions (see Merritt et al., 2013 for a review) and reductions in cortical surface area have been linked to negative symptoms (Padmanabhan et al., 2015). Together, evidence for divergent neuropathological deficits supports the notion of distinct symptomologies.

In addition, neuropsychological assessments have shown discriminate validity between subscale scores of positive and negative symptoms (Kay et al., 1987; Lançon et al., 2000; Peralta and Cuesta, 1994a). Accordingly, it is not surprising that the effectiveness of antipsychotic drugs (APDs) varies between symptom types (Leucht et al., 2009). Antipsychotics are generally classified as first generation (FGAs: e.g., Haloperidol) or second generation (SGAs: e.g., Risperidone) due to SGAs targeting serotonin receptors (Kuroki et al., 2008) and producing fewer side effects (Rummel-Kluge et al., 2012). Both variants are dopamine antagonists (exception: Aripiprazole), however, through which dopamine transmission is inhibited by limiting access to dopamine D2 receptors (Ellenbroek, 2012a,b). As a result, both classes of APDs have been shown to be effective for reducing positive symptoms (Leucht et al., 2009). Negative symptoms, in contrast, are less responsive to both classes of APDs (Millan et al., 2014) and the early promise of drugs that target glutamate transmission has been tempered (Kingwell, 2014). This is unfortunate because individuals with schizophrenia that suffer from negative symptoms have particularly poor function (Rabinowitz et al., 2012), quality of life (Packer et al., 1997), and social relationships (Ho et al., 1998). Developing and especially evaluating experimental therapeutics aimed towards the goal of alleviating negative symptoms is therefore a mental health priority (Kirkpatrick et al., 2006).

Oxytocin (OT) is a neuropeptide that has been shown to mediate prosocial behaviors, such as alloparental care (Bales et al., 2007, 2004) and pair-bond formation (Cho et al., 1999), in non-human animals. Administering intranasal OT (IN-OT) in healthy and clinical populations reportedly improves aspects of social cognition, including emotion recognition (Guastella et al., 2010; Lischke et al., 2012) and theory of mind (Domes et al., 2007; Pedersen et al., 2011a,b). Relationships between oxytocin and psychiatric symptoms have also been explored in individuals with schizophrenia (see Feifel et al., 2016 for a review). For instance, peripheral OT levels are predictive of positive symptoms and general psychopathology in females with schizophrenia (Rubin et al., 2010). In contrast, there is evidence for an inverse correlation between cerebrospinal fluid OT levels and negative symptoms in males with schizophrenia (Sasayama et al., 2012). Additionally, two single nucleotide polymorphisms (i.e., rs53576 and rs2740204) within the oxytocin receptor gene (OXTR) have been linked to schizophrenia (Montag et al., 2013). Due to converging evidence in non-human animals, healthy human populations, and those with schizophrenia OT has been identified as potentially having therapeutic properties (Striepens et al., 2011). As a result, numerous randomized controlled trials (RCTs) have investigated the efficacy of IN-OT in reducing symptoms of schizophrenia.

In the extent literature, evidence for a positive effect of oxytocin in RCTs has been mixed. In the present study we therefore performed a meta-analysis on RCTs in which IN-OT was used as a treatment for schizophrenic symptoms (i.e., negative and positive) as well as general psychopathology which is often comorbid with both aspects of symptomology. We also looked at the sum of the three symptom types which together represents an overall measure of schizophrenia. To date, three meta-analyses have been conducted on similar topics (Gumley et al., 2014; Hofmann et al., 2015a; Oya et al., 2015). While preparing the current study, however, we discovered several errors in two of these meta-analyses (Gumley et al., 2014; Hofmann et al., 2015b). For instance, some of the original studies reported a negative effect of IN-OT but were coded as positive in these meta-analyses. Indeed, while they combined to report eight significant effects of IN-OT on psychiatric symptoms, we reproduced their methods and showed every outcome was actually non-significant (Williams and Burkner, 2016a,b). While the third meta-analysis on this topic did not necessarily have errors (Oya et al., 2015), they computed meta-analytic estimates based on post-treatment scores which does not answer the question of whether IN-OT actually reduced symptoms. With this approach, the IN-OT group was reported to have less negative symptoms than the placebo group in studies where treatment was administered on a daily basis.

In addition to including all RCTs to date, the present investigation offers several advantages when compared to previous meta-analyses: (1) We used a multivariate analysis which allows for comparisons between symptoms and accounts for correlations between symptoms; (2) We explicitly answered the question of whether IN-OT reduces symptoms by reporting standardized mean change using raw score standardization (SMCR); (3) We used a fully Bayesian framework that allows prior information to be incorporated, which improves precision of estimates and allows assessment of evidence in favor of the null hypothesis (i.e.,

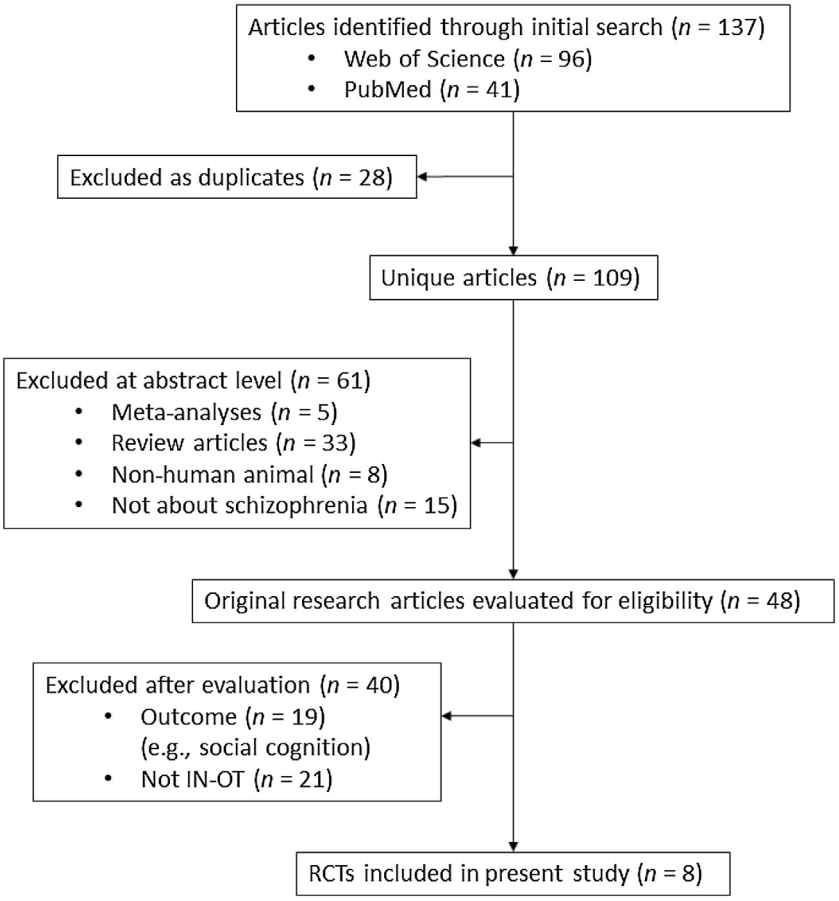

Fig. 1. Flowchart illustrating the literature search process in accordance with the PRISMA guidelines.

no effect of oxytocin) using Bayes factors; and (4) We addressed inconsistencies in the primary studies (Appendix A.1) and previous meta-analyses (Appendix A.2). Thus, we performed an updated multivariate Bayesian meta-analysis to determine whether IN-OT is effective for reducing symptoms of schizophrenia and to determine whether IN-OT has advantages specifically for treating negative symptoms when compared to positive symptoms and general psychopathology.

2. Methods

2.1. Inclusion criteria and search strategy

We preformed the current study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Moher et al., 2010). We used the Patient, Intervention, Comparator, and Outcome (PICO) strategy as a guide for conducting a systematic literature review (*patients*: diagnosed with schizophrenia; *intervention*: IN-OT administration; *comparator*: placebo with same ingredients as intervention excluding OT; *outcome*: negative (primary outcome)), positive, general psychopathology, and overall symptoms as measured by subscales within the Positive and Negative Syndrome Scale (PANSS), the Clinical Assessment Interview for Negative Symptoms (CAINS), the Scale for the assessment of negative/positive symptoms (SANS/SAPS), and the Brief Psychiatric Rating Scale (BPRS). In addition to meeting the PICO criteria, only double-blind RCTs were eligible for inclusion.

The initial search was conducted in the Web of Science and PubMed for peer-reviewed research articles that were published up to June 22, 2016 using the search term "oxytocin AND schizophrenia." This search yielded 436 hits between both databases. To narrow the search, we then used the search term "oxytocin AND schizophrenia AND intranasal" through which 137 studies were found. Of the 137 studies, 28 were excluded as duplicates. We then excluded 61 articles for the following reasons: meta-analysis, review, non-human animal, and for not being about schizophrenia (Fig. 1). Of the remaining 48 articles that were evaluated for eligibility, 19 were excluded because of the outcomes measured and 21 were excluded because IN-OT was not administered. In total, we identified seven RCTs in which treatment was administered on a daily basis. While Davis et al. (2014) only administered IN-OT on days when social cognitive training took place, we included this study because another RCT used a similar method of training. Accordingly, this allowed for investigating the moderating effect of social cognitive training. Through sensitivity analyses, meta-analytic estimates excluding Davis et al. (2014) were computed which provided an estimate for studies that administered IN-OT daily. Together, eight RCTs (primary studies) were thus used in the present analyses.

2.2. Data extraction and outcomes

Data were extracted from the primary studies and then processed into effect sizes and their corresponding variances (see Section 2.3). Corresponding authors were contacted when the primary studies did not include the data needed for computing SMCR effects sizes or when relevant background information was not provided. Dr. Dagani provided information concerning antipsychotic medication and dosages (Dagani et al., 2016), whereas Dr. Gibson provided baseline data (i.e., pre-treatment) for overall symptom

scores and standard deviations for oxytocin and placebo groups (Gibson et al., 2014a,b).

In total, eight studies reported on negative symptoms using a variety of psychometric scales: PANSS negative symptom subscale scores (Dagani et al., 2016; Feifel et al., 2016; Gibson et al., 2014a,b; Modabbernia et al., 2013; Pedersen et al., 2011a,b); SANS (Cacciotti-Saija et al., 2015; Lee et al., 2013); CAINS (Davis et al., 2014). Positive symptoms were obtained from six studies: PANSS positive symptoms subscale scores (Dagani et al., 2016; Feifel et al., 2016; Gibson et al., 2014a,b; Modabbernia et al., 2013; Pedersen et al., 2011a,b); SAPS (Cacciotti-Saija et al., 2015). General psychopathology scores were obtained from five studies: PANSS general psychopathology subscale (Dagani et al., 2016; Feifel et al., 2016; Gibson et al., 2014a,b; Modabbernia et al., 2013; Pedersen et al., 2011a,b). For consistency with previous meta-analyses, an overall symptom score of schizophrenia was obtained from primary studies as a combined total of negative symptoms, positive symptoms, and general psychopathology.

2.3. Moderator variables

We also obtained study characteristics for moderator analyses that were of theoretical interest. Both animal and human studies have indicated that OT may have sex dependent effects. Furthermore, OT levels in males and female with schizophrenia are associated with different aspects of symptomology. While predictive of positive symptoms in males, OT levels are associated with negative symptoms in females. As such, the proportion of males in each study was used as a potential moderator. As OT dosage varied between studies, this was also included as a moderator. Demographic variables, including age of participants and study country, were also obtained for moderator analyses. Unfortunately, descriptions of medications were to varied to assess the moderating effect of antipsychotic drugs.

2.4. Statistical analysis

To estimate the influence of oxytocin on schizophrenic symptoms, we used two types of effect sizes. First, the standardized mean difference (SMD; also known as Hedges' g) was computed for post-treatment to facilitate comparison with the previous meta-analyses, which reported only SMD estimates. Second, the standardized mean change using raw score standardization (SMCR) was computed (Morris and DeShon, 2002). The SMCR, unlike SMD, not only contrasts treatment and control group, but also controls for possible differences in the pre-treatment values. This is achieved by (1) computing the standardized mean difference between two time points (i.e,. pre- and post-treatment) separately for treatment and control group and (2) contrasting the two groups with respect to this difference (see Appendix B for the computational details). The SMCR provides a better estimate of the treatment effect, but it requires knowledge of the correlations of outcomes across time points to compute its variance (Morris and DeShon, 2002). As these correlations were rarely reported in the primary studies, they were set to $r = 0.5$ in order to be similar to correlations typically obtained in schizophrenia studies (e.g., see the *Schizo_PANSS* data in the R package *Surrogate*; Buyse et al., 2016).

Schizophrenic symptoms are typically divided into two conceptually different constructs—positive and negative symptoms. In addition, general psychopathology is usually also assessed. The sum score of the three constructs then constitutes an overall symptom score of schizophrenia. Previous meta-analyses either investigated primarily the overall symptom score (Hofmann et al., 2015b) or all symptom types separately (Gumley et al., 2014; Oya et al., 2015). The former approach is problematic because it ignores possible differences between symptom types. The latter approach – while preferable to the former – still ignores substantial correlations between symptom types (Peralta and Cuesta, 1994b). We thus performed multivariate meta-analysis, which allows estimating the effect of oxytocin on the three schizophrenic symptom types consistently within one model. This approach also allows testing differences between the effects of IN-OT on different symptom types.

Since studies differ more or less in their experimental design, outcome assessment, and treatment properties there will likely be some heterogeneity between outcomes of different studies (Higgins and Thompson, 2002). Statistical heterogeneity in particular occurs when the true effects of the different studies show a larger variation than it would be expected due to random error or by chance (Deeks et al., 2008; Higgins and Thompson, 2002). With regard to the interpretation of the results and the conclusions that can be drawn from a meta-analysis, it is important to assess the heterogeneity between the studies (Huedo-Medina et al., 2006). Therefore, a (multivariate) hierarchical model was assumed not only allowing us to estimate the pooled effect sizes and corresponding credible (i.e. Bayesian confidence) intervals, but also the between-study variances $\boldsymbol{\tau}^2$ and standard deviations $\boldsymbol{\tau}$ of each symptom type. To analyze the influence of potential moderators, meta-regression models (Thompson and Higgins, 2002) were applied separately for each moderator.

All of our models where fitted in a fully Bayesian framework for two reasons. First, we wanted to incorporate some prior information into our models (specifically for the between standard deviations $\boldsymbol{\tau}$), in order to facilitate hierarchical shrinkage of study estimates which helps in improving precision of the obtained overall estimates (Gelman, 2006). Second, it allows assessing the evidence for the null hypothesis (i.e. no effect of oxytocin) via Bayes-factors (Jeffreys, 1998; Wagenmakers et al., 2010), an approach that is not available when fitting models in a frequentist framework. For mathematical details on the applied meta-analytic model as well as specification of priors see Appendix C. Priors were chosen to be only weakly informative so that their influence on the meta-analytic estimates is relatively small. In addition to credible intervals and Bayes factors, p-values were reported in order to reach a broader audience.

Potential for publication bias was examined using funnel plots (Sterne and Egger, 2001; Sterne et al., 2011) and the trim and fill method (Duval and Tweedie, 2000). The alpha-level of all statistical tests was set to $\alpha = 0.05$. All computation was done in R (R Core Development Team, 2016). The package *metafor* (Viechtbauer, 2010) was used for the effect size computation, while the package *brms* (Bürkner, 2016) – allowing to fit Bayesian multilevel models (including meta-analytic models) using *Stan* (Carpenter et al., 2015) – was used for the actual analysis.

3. Results

3.1. Study characteristics

Across all eight RCTs, 238 adults with Schizophrenia were randomized between experimental group receiving oxytocin and control group receiving placebo (doses: 24–80 IU per day). Sample sizes ranged from 14 to 52 patients. Summarized over all studies, the mean age was 34.1 years and 79% of the participants were male. All studies were published in English and were not sponsored by the pharmacological industry. Detailed study characteristics can be found in Table 1.

Table 1
Main characteristics of the included primary studies.

							Pre-treatment		Post-Treatment	
First Author	Year	Country	N EG/CG	Mean Age EG/CG	% Male EG/CG	Symptom	Mean EG/CG	SD EG/CG	Mean EG/CG	SD EG/CG
Cacotti-Saija	2015	Australia	27/25	21.5/22.3	67%/72%	negative	9.40/10.92	4.47/3.74	8.49/9.48	4.83/3.78
						positive	5.56/4.08	4.23/3.56	4.63/2.48	3.68/2.92
Dagani	2016	Italy	16/16	30.4/30.4	81%/81%	negative	27.30/22.50	5.60/5.00	22.60/18.00	7.10/3.60
						positive	15.60/15.40	4.20/4.70	13.50/13.50	3.40/4.50
						general	42.30/39.10	4.60/7.30	36.40/34.20	8.70/7.50
						overall	85.20/77.00	8.80/10.50	72.50/65.70	15.80/12.90
Davis	2014	USA	11/11	42.8/37	100%/100%	negative	22.00/19.10	10.20/6.90	21.10/17.80	11.60/7.10
						overall	28.30/33.50	6.60/10.60	33.60/38.50	8.90/13.30
Feifel	2010	USA	15/15	48/48	80%/80%	negative	20.20/21.80	4.70/4.70	18.50/20.70	4.50/4.30
						positive	21.70/22.80	4.10/5.20	19.90/21.90	5.20/4.80
						general	38.80/37.50	7.60/6.60	34.80/36.40	6.90/7.30
						overall	81.50/82.15	12.40/11.10	73.60/79.10	13.60/12.90
Gibson	2014	USA	8/6	38.9/35.7	75%/83%	negative	19.75/17.50	4.10/4.46	17.25/17.70	4.20/3.66
						positive	16.88/22.50	4.61/5.17	14.00/18.50	3.34/6.22
						general	34.75/41.00	7.01/9.03	29.88/32.67	4.91/4.13
						overall	71.38/81.00	12.90/14.81	61.38/68.33	9.12/8.78
Lee	2013	USA	13/15	44.7/35.1	69%/73%	negative	31.19/36.00	7.85/8.53	30.54/35.27	7.81/8.50
						overall	37.31/34.00	7.24/7.78	36.51/29.87	7.96/6.44
Modabbernia	2013	Iran	20/20	32.3/33.2	85%/80%	negative	25.00/24.40	2.90/2.90	23.70/24.10	2.90/2.90
						positive	23.30/24.20	3.00/3.10	20.00/23.50	3.00/3.10
						general	41.20/41.90	4.20/5.30	39.20/41.30	4.20/5.30
						overall	89.50/90.50	6.70/8.30	82.80/88.90	6.70/8.30
Pederson	2011	USA	11/9	39/35.8	82%/89%	negative	21.00/19.11	4.12/3.98	18.91/18.00	3.81/3.67
						positive	20.46/21.67	5.80/6.91	17.73/20.44	5.44/5.50
						general	40.64/38.22	7.84/10.41	35.18/37.22	6.48/10.08
						overall	82.90/78.89	13.59/16.75	71.80/75.67	11.29/13.73

Note: EG = experimental group receiving oxytocin; CG = control grouping receiving placebo.

Table 2
Main results of the meta-analysis.

Effect Size	Symptom Type	# Studies	Estimate	*95%-CI*	*p*-value	BF_{01}	τ	*95%-CI* of τ
SMCR	Negative	8	−0.06	[−0.34, 0.22]	0.683	3.29	0.13	[0.00, 0.41]
	Positive	6	−0.16	[−0.49, 0.19]	0.354	1.99	0.29	[0.01, 0.61]
	General	5	−0.24	[−0.59, 0.14]	0.192	1.09	0.18	[0.01, 0.57]
SMD	Negative	8	−0.02	[−0.32, 0.28]	0.848	3.51	0.20	[0.01, 0.56]
	Positive	6	−0.23	[−0.71, 0.27]	0.305	1.23	0.50	[0.12, 1.09]
	General	5	−0.19	[−0.53, 0.17]	0.279	1.54	0.16	[0.00, 0.49]
SMCR	Overall	7	−0.19	[−0.55, 0.18]	0.297	1.54	0.22	[0.01, 0.67]
SMD	Overall	7	−0.13	[−0.53, 0.3]	0.519	2.02	0.42	[0.04, 1.00]

Note: SMD = standardized mean difference; SMCR = standardized mean change with raw score standardization; CI = credible interval; τ = between-study standard deviation; *p*-values are two-tailed; BF_{01} indicates the evidence in favor of the null hypothesis that oxytocin has no effect on schizophrenic symptoms.

3.2. Meta-analysis

Except for the primary meta-analysis, we only display analyses of the SMCR effect sizes in the following in order to simplify presentation of the results. Corresponding analyses of the SMD effect sizes – yielding very similar results – can be found in Appendix D. Forest plots visualizing the obtained effects of each study are displayed in Fig. 2. Multivariate hierarchical meta-analyses revealed no significant effect of oxytocin on schizophrenic symptom types (see Table 2). Moreover, Bayes factors indicated moderate evidence in favor of the null hypothesis for negative symptoms ($BF_{01} = 3.37$), while Bayes factors were inconclusive for positive symptoms ($BF_{01} = 1.81$) and general psychopathology ($BF_{01} = 1.02$). There were no substantial differences between effect sizes for negative and positive symptoms ($SMCR_{diff} = 0.10$, $CI = [-0.34, 0.54]$, $p = 0.621$, $BF_{01} = 2.90$), negative symptoms and general psychopathology ($SMCR_{diff} = 0.19$, $CI = [-0.20, 0.58]$, $p = 0.323$, $BF_{01} = 2.06$) as well as positive symptoms and general psychopathology ($SMCR_{diff} = 0.08$, $CI = [-0.38, 0.56]$, $p = 0.739$, $BF_{01} = 2.97$). Meta-analyses of overall symptoms did not show a significant effect of oxytocin (see Table 2).

3.3. Moderator analysis

The following variables were analyzed as potential moderators: *Mean age of patients in the oxytocin/placebo group*, *percentages of male patients in the oxytocin/placebo group*, *therapy duration*, *oxytocin dosage per ingestion/day*, *administration interval*, *social training*, and *country*. To achieve an acceptable amount of statistical power, moderator variables were analyzed separately and their effects were not assumed to vary between symptom types. As shown in Table 3, no moderator could explain a significant amount of heterogeneity between primary studies.

3.4. Sensitivity analysis

In order to investigate the robustness of the above discussed effects, several additional analyses were performed. First, potential for publication bias was investigated. According to the funnel plots displayed Fig. 3, there seems to be little evidence of publication bias. Results obtained by the trim and fill method confirm this finding (not more than one study missing on either left or right side of

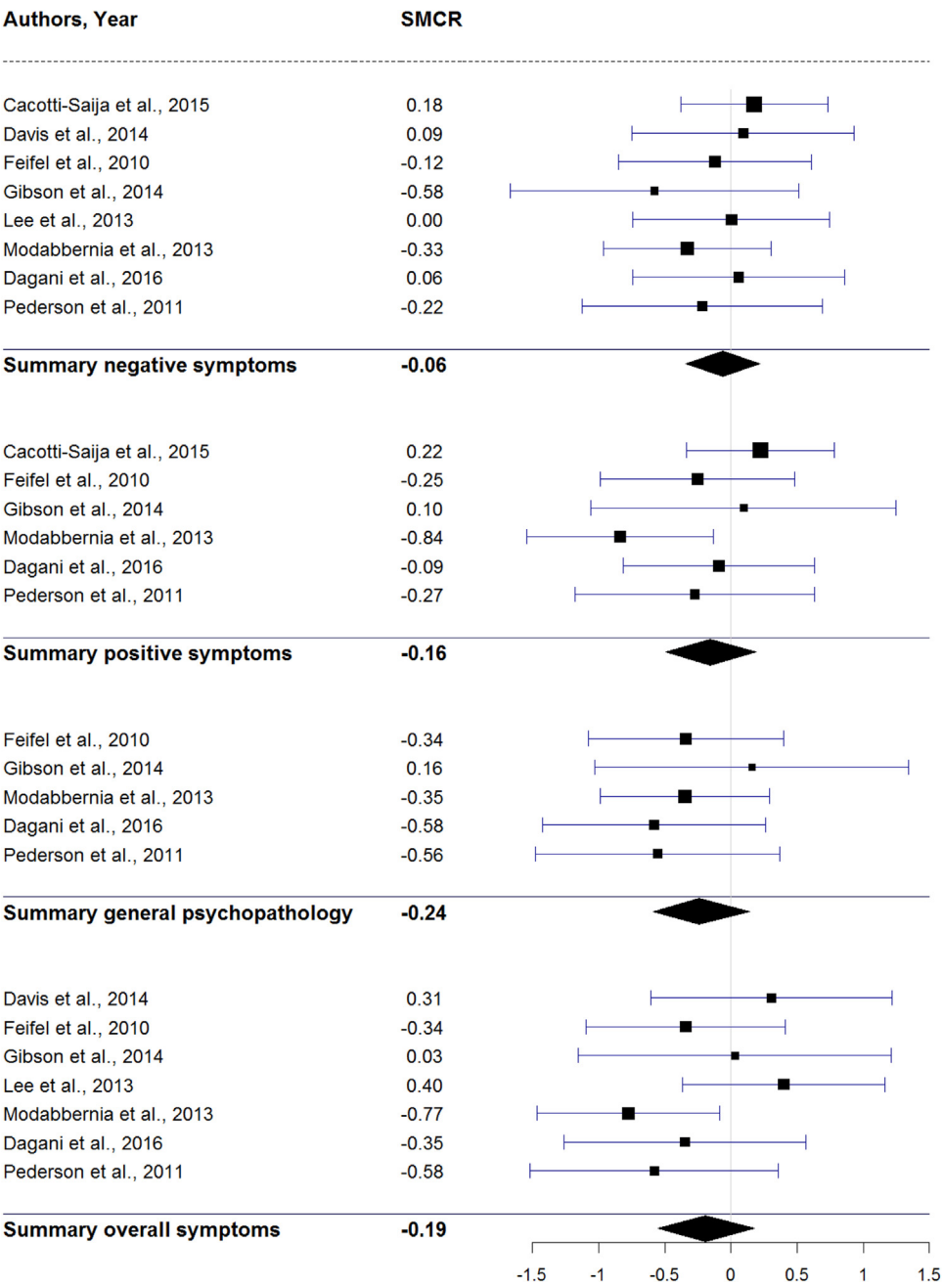

Fig. 2. Forest plots of SMCR effect sizes separated after symptoms type.

Table 3
Moderator analysis of SMCR effect sizes.

Moderator	Estimate	*95%-CI*	*p*-value
Mean Age EG (years)	−0.01	[−0.02, 0.01]	0.331
Mean Age CG (years)	−0.01	[−0.02, 0.01]	0.287
% Males EG	−0.35	[−1.08, 0.37]	0.347
% Males CG	−0.28	[−0.99, 0.45]	0.456
Therapy duration (days)	−0.01	[−0.05, 0.04]	0.694
OT doses per ingestion (IU)	−0.01	[−0.02, 0.00]	0.139
OT doses per day (IU)	−0.01	[−0.01, 0.00]	0.099
Social training (yes vs. no)	0.37	[−0.10, 0.85]	0.129
Country (USA vs. other)	−0.07	[−0.50, 0.35]	0.726

Note: SMCR = standardized mean change with raw score standardization; CI = credible interval; EG = experimental group receiving oxytocin; CG = control grouping receiving placebo; OT = oxytocin; *p*-values are two-tailed.

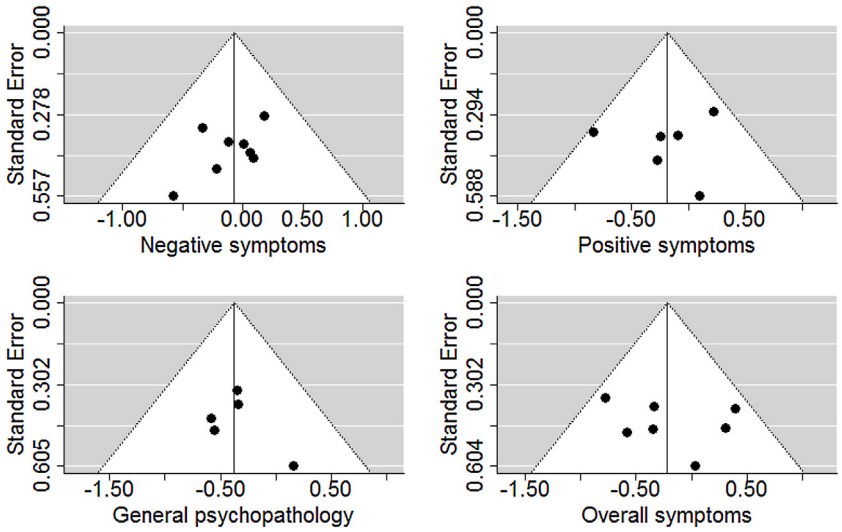

Fig. 3. Funnel plots of SMCR effect sizes separated after symptoms type.

the funnel). However, one should keep in mind that it is difficult to assess publication bias based on only a few studies as in the present case.

To investigate the influence of single studies on the obtained meta-analytic effects, leave-one-out analyses were conducted. The differences between effects obtained by the leave-out–out analysis and the complete analysis were within [−0.12, 0.13] for positive symptoms, [−0.05, 0.05] for negative symptoms, and [−0.06, 0.07] for general psychopathology (see Table 4). Furthermore, all effects remained non-significant after exclusion of one study.

4. Discussion

The present study is the first meta-analysis to use multivariate Bayesian methods to elucidate the efficacy of IN-OT on reducing symptoms in schizophrenia. In comparison to previous meta-analyses, this improved methodology specifically allowed for: (1) comparisons of symptom types to determine whether oxytocin had benefits for treating negative symptoms when compared to positive and general symptoms; (2) incorporation of prior information into the between study variance which increased power by improving the precision of our estimates; (3) measurement of evidence in favor of the null hypothesis (i.e., no effect of oxytocin); (4) explicit inclusion of baseline scores in our final estimate through the use SMCR. Using these improved methods, the meta-analytic estimates on all aspects of symptomology were non-significant and there was moderate evidence for no effect of IN-OT on negative symptoms. Accordingly, IN-OT was not especially effective for treating negative symptoms when compared to positive symptoms and general psychopathology.

Table 4
Leave-one-out analysis of SMCR effect sizes.

Excluded Study	Symptom Type	Estimate	*95%-CI*	*Diff*
Cacotti-Saija et al. (2015)	Negative	−0.11	[−0.41, 0.20]	−0.05
	Positive	−0.28	[−0.67, 0.13]	−0.12
	General	−0.28	[−0.64, 0.10]	−0.04
Davis et al. (2014)	Negative	−0.07	[−0.38, 0.22]	−0.01
	Positive	−0.16	[−0.51, 0.18]	0.00
	General	−0.25	[−0.61, 0.12]	0.01
Feifel et al. (2010)	Negative	−0.05	[−0.34, 0.25]	0.01
	Positive	−0.14	[−0.52, 0.25]	0.02
	General	−0.21	[−0.62, 0.22]	0.03
Gibson et al. (2014a,b)	Negative	−0.02	[−0.31, 0.27]	0.04
	Positive	−0.18	[−0.55, 0.20]	−0.02
	General	−0.30	[−0.68, 0.07]	−0.06
Lee et al. (2013)	Negative	−0.07	[−0.36, 0.23]	−0.01
	Positive	−0.16	[−0.51, 0.18]	0.00
	General	−0.25	[−0.60, 0.13]	−0.01
Modabbernia et al. (2013)	Negative	−0.01	[−0.31, 0.29]	0.05
	Positive	−0.03	[−0.39, 0.31]	0.13
	General	−0.23	[−0.66, 0.24]	0.01
Dagani et al. (2016)	Negative	−0.07	[−0.36, 0.21]	−0.01
	Positive	−0.17	[−0.56, 0.24]	−0.01
	General	−0.17	[−0.57, 0.25]	0.07
Pederson et al. (2011)	Negative	−0.05	[−0.33, 0.24]	0.01
	Positive	−0.15	[−0.53, 0.22]	0.01
	General	−0.20	[−0.59, 0.21]	0.04

Note: SMCR = standardized mean change with raw score standardization; CI = credible interval; Diff = Difference between estimates of the leave-out–out analysis and the complete analysis displayed in Table 1.

4.1. Comparison to previous meta-analyses

While using a traditional measure of evidence (i.e., *p*-values), we found that there were no significant effects in which oxytocin was not superior to placebo for reducing positive symptoms, negative symptoms, general psychopathology, or overall symptomology. This stands in contrast to previous meta-analyses (Gumley et al., 2014; Hofmann et al., 2015b; Oya et al., 2015), each of which reported at least one beneficial effect. In addition to the errors we discovered (Williams and Burkner, 2016a,b), the null findings in the present study cannot be attributed to differing effect sizes used. While our primary effect size was SMCR, we also computed SMD (the quantity used in the previous meta-analyses) which also showed non-significant effects of oxytocin. In three of the primary studies (Cacciotti-Saija et al., 2015; Dagani et al., 2016; Gibson et al., 2014a,b), however, symptoms reduced over time for both the oxytocin and placebo group. That is, symptoms improved for both study groups over the course of the trial. As such, the primary effect size reported in the present study (i.e., SMCR) is likely most appropriate because it directly answers the research question of interest. In other words, our meta-analytic estimates assess change from baseline and whether that change was greater for the OT group than the placebo group.

Based on the literature concerning oxytocin's facilitation of social behavior in non-human animals, IN-OT has been suggested as having therapeutic properties specifically for treating negative symptoms (e.g., social deficits). In addition to a non-significant *p*-value, there was moderate evidence in favor of the null for negative symptoms (i.e., no effect of oxytocin). In contrast, a previous meta-analysis reported that IN-OT reduced negative symptoms but this effect was moderated by administration interval (i.e., daily vs. day of training). Since only one of the primary studies administered IN-OT on select days (Davis et al., 2014), we did not conduct a similar moderator analysis. It should be noted that, when excluding Davis et al. (2014) through leave-one-out analyses, we obtained meta-analytic estimates for studies that administered treatment on a daily basis and these effects were non-significant (Table 4). Using multivariate techniques, we further explored the hypothesized relationship between oxytocin and negative symptoms. Comparisons between symptom types were non-significant and the Bayes factors were inconclusive such that IN-OT was not especially beneficial for reducing negative symptoms.

A prior meta-analysis (Oya et al., 2015) found a moderator effect of study duration for general and total symptoms. This difference may be due to how duration was measured. While duration was a continuous variable in the present study, the previous meta-analysis dichotomized duration (>3 weeks and $\leq$3 weeks) which may have adversely affected the precision of the estimate (Royston et al., 2006) or inflated the type one error rate (Austin and Brunner, 2004). They also reported that a combination of IN-OT and the patient's antipsychotic medication (i.e., Risperidone) may work in concert to reduce symptoms. Although based a single study that we identified as an out outlier (Appendix A), commonly used antipsychotic drugs (APDs) inhibit dopamine transmission by acting as receptor antagonists (Ellenbroek, 2012a,b; Kuroki et al., 2008). However, access to dopamine D2 receptors is necessary for OT-induced pro-social behavior in animals (Liu and Wang, 2003; Love, 2014). Accordingly, interactions between OT and APDs should be investigated in future studies.

4.2. Moderator analyses

While investigating potential moderators, we analyzed all symptom types together which was done to increase statistical power. However, none of the moderators contributed towards reducing symptomology (Table 3). Most notably, we found that administering IN-OT for three weeks or 16 weeks did not moderate the effect of IN-OT. Despite extensive data suggesting sexual dimorphic effects of OT in animals and human (Cushing and Carter, 2000; Domes et al., 2010), the proportion of males in a given sample did not moderate the effects of IN-OT. However, 79% of the combined sample was male which makes it difficult to determine whether IN-OT is beneficial for women with schizophrenia. While there was variability in dosage, ages of participants, and study country, none of these variables explained a significant amount of between study heterogeneity (Table 3). However, due to small sample sizes it would be premature to draw definitive conclusions from these analyses.

4.3. Comparison to relevant literature

We did not find evidence for an effect of IN-OT, which adds to the current debates surrounding this literature. IN-OT research in healthy human's is often portrayed as settled science, for instance, but this has recently been called into questions by several authors (Leng and Ludwig, 2016; Nave et al., 2015; Walum et al., 2016). Most notably, Lane et al. (2016) published a paper in which the file drawer (e.g., unpublished null results) problem became apparent. When using IN-OT as an experimental manipulation across 13 outcomes (e.g., empathy and trust), only five articles were accepted for publication (i.e., a publication rate of 38.5%). They then preformed a meta-analysis on their data (published and unpublished) and showed the effect sizes were incredibly close to zero (overall: Cohen's $d = 0.003$; behavior: $d = 0.09$; cognition: $d = 0.10$). It is unfortunate that these null results were not initially accepted for publication because meta-analyses on these same topics (Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012) are often used as evidence in favor of IN-OT (Quintana and Woolley, 2016). What is less appreciated, however, is that meta-analyses are dependent on published findings (Thornton and Lee, 2000). As such, Lane et al. (2016) calls into question the conclusions from which the potential therapeutic properties of oxytocin have been derived.

Our null results should also bring attention to the fact that the mechanisms by which OT influences behavior, cognition, or psychiatric symptoms are poorly understood (Viero et al., 2010). There is inconsistent evidence, for instance, of whether (Freeman et al., 2016) and how much IN-OT enters cerebrospinal fluid (CSF; see here for review: Leng and Ludwig, 2016). For studies that reported an increase of oxytocin in CSF, it is estimated that only a fraction of the dose reaches CSF within one hour (Leng and Ludwig, 2016). Additionally, interactions within the oxytocin–oxytocin receptor system are complex (Bussolati and Cassoni, 2011). In order for IN-OT to have a psychopharmacological effect it must first bind to it receptors through which intracellular signaling pathways become activated (Viero et al., 2010). In rat dams, for instance, OTR activation results in improved spatial memory through the Mitogen-activated protein kinase (MAPK) signaling pathway in which phosphorylation of the cAMP response element-binding protein occurs (CREB; Tomizawa et al., 2003). Furthermore, a similar intracellular response to microinfusions of OT in the paraventricular nucleus of male rats was shown to reduce anxiety (Blume et al., 2008). These studies administered OT directly into the brain, however, so it remains unclear whether IN-OT administration activates these same signaling pathways.

4.4. Limitations

The present study does have several limitations. First, as is the case with most meta-analyses, our estimates are dependent upon the published literature. Although we did not discover publication bias, it should further be noted that bias was only assessed

in published literature which does not mean it is completely absent. Second, dosage and administration protocols were not consistent among studies. We conducted moderator analyses on these variables, each of which produced a negligible effect. Third, schizophrenia is a heterogeneous disorder in which a spectrum of symptoms exists (Kendler et al., 1995; Sullivan et al., 2003) and we were unable to analyze differing treatment effects among individuals with certain symptom profiles. Fourth, OT likely has complex relationships with antipsychotic drugs. We were not able to investigate this possibility, however, because descriptions of medication regimens were too varied in the primary studies. Fifth, effects of OT often depended on sex. Despite performing a moderator analysis on the proportion of males in each study, there were far too few females to draw meaningful conclusions about possible sex differences of IN-OT on schizophrenic symptoms. Sixth, as Bayesian methods are less commonly used, this unfamiliarity may be seen as a limitation. To address this, we also provided *p*-values so our results could reach a broader audience. Seventh, the present meta-analysis was based on only eight RCTs with a combined sample size of 238 patients, which is likely too small for a final evaluation of the effect of oxytocin on schizophrenic symptoms.

5. Conclusion

In conclusion, our results suggest that oxytocin does not improve any aspect of symptomology schizophrenia. However, it remains unclear whether these findings are just due to absence of evidence or really indicate evidence of absence. In support for the latter, the largest evidence in favor of the null hypothesis of no effect was for the negative symptoms, which – according to theory – were expected to improve most through OT. While the evidence for OT's effects on behavior in animals is substantial, direct routes of administration are often used in animal research. Accordingly, these null results might urge the field forward and towards investigating more direct routes of oxytocin administration. This is especially important because of the lack of effective treatments for negative symptoms in schizophrenia.

Conflict of interest

We declare no conflict of interests.

Contributors

Both authors contributed equally and to all aspects of this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.10.013.

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