Hormones and Behavior 146 (2022) 105268

Contents lists available at ScienceDirect

Hormones and Behavior

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

The effect of intranasal oxytocin on processing emotional stimuli during alcohol withdrawal: A randomized placebo-controlled double-blind clinical trial

Katrine Melby [a,*], Olav Spigset [a,c], Rolf W. Gråwe [d,e], Trond O. Aamo [a,b], Daniel S. Quintana [f,g,h]

[a] Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway
[b] Blue Cross Lade Addiction Treatment Centre, Trondheim, Norway
[c] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology – NTNU, Trondheim, Norway
[d] Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology – NTNU, Trondheim, Norway
[e] Department of Research and Development, Division of Psychiatry, St. Olav University Hospital, Trondheim, Norway
[f] Department of Psychology, University of Oslo, Oslo, Norway
[g] NevSom, Department of Rare Disorders, Oslo University Hospital, Oslo, Norway
[h] Norwegian Centre for Mental Disorders Research (NORMENT) and KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway

ARTICLE INFO

Keywords:
Alcohol withdrawal
Oxytocin
RMET
Theory of mind
Social cognition

ABSTRACT

Alcohol dependence is associated with difficulties in processing emotional stimuli, which can lead to interpersonal problems. The neuropeptide oxytocin has been shown to modulate the processing of emotional stimuli, however, oxytocin treatment has not yet been examined in patients with withdrawal symptoms during alcohol detoxification. The aim of the present study was to investigate the effect of oxytocin on the reading the mind in the eyes test (RMET), which indexes theory of mind ability, during a three-day period of alcohol detoxification at an addiction treatment centre in Norway. We performed a randomized, double-blind, placebo-controlled trial in 39 patients fulfilling criteria for ICD-10 diagnosis of alcohol dependence admitted for alcohol detoxification and withdrawal treatment. Participants were randomized to receive either intranasal oxytocin (24 IU) or placebo, twice daily for three days. We evaluated RMET performance on day 2 and day 3 of detoxification and differences in RMET scores between day 2 and day 3 of detoxification. Frequentist and Bayesian statistical inference suggested that oxytocin administration during alcohol withdrawal in alcohol-dependent patients did not improve RMET performance. However, exploratory analyses provided preliminary evidence that oxytocin might improve performance on the RMET negative emotion subscale (uncorrected p value = 0.038), and that oxytocin treatment might show the most promise for those with high levels of alcohol consumption (i.e., ≥20 alcohol units per day; uncorrected p value = 0.023). Moreover, alcohol consumption levels significantly predicted RMET performance on day 2, but not on day 3, of withdrawal.

1. Introduction

Alcohol dependence is associated with emotional dysregulation, which can contribute to interpersonal relationship difficulties, treatment dropout and post-treatment relapse (Foisy et al., 2007). Improvement of interpersonal relations is critical to ensure success of a detoxifixation treatment (Marlatt, 1996).

The processing of emotional stimuli in alcohol dependence is commonly assessed by the Reading the Mind in the Eyes Test (RMET). Because the RMET consists of pictures of emotion expressions from the eyes of faces, it is suggested to be a more sensitive measure of theory of mind compared to other measures. Individuals with alcohol use disorder (AUD) perform worse than controls on affective theory of mind tasks, which may be due to the symptomatology of AUD as well as a possible consequence of specific alcohol related brain damage (Onuoha et al., 2016). Findings also indicate that patients with alcohol dependence have impaired abilities to recognise positive, negative and complex emotions (Maurage et al., 2011; Nandrino et al., 2014; Thoma et al.,

* Corresponding author at: St. Olavs Hospital HF, Avdeling for klinisk farmakologi, Postboks 3250 Torgarden, NO-7006 Trondheim, Norway.
E-mail address: Katrine.melby@stolav.no (K. Melby).

https://doi.org/10.1016/j.yhbeh.2022.105268
Received 21 February 2022; Received in revised form 15 September 2022; Accepted 24 September 2022
Available online 13 October 2022

2013).

Oxytocin is a neuropeptide and hormone primarily produced in the hypothalamus that has been proposed to exert both social and anxiolytic effects in human and non-human mammals (King et al., 1736). RMET performance has been shown to be enhanced after oxytocin administration in a neurotypical population (Domes et al., 2007) and in alcohol dependent individuals (Mitchell et al., 2016), although the latter finding was not replicated in a subsequent study (Radke and de Bruijn, 2015).

There is growing research interest as to whether the social and anxiolytic effects of oxytocin can be useful in treatment during different stages of alcohol use disorder in order to alleviate withdrawal symptoms, craving, and relapse (Frileux et al., 2020; King et al., 2020). Researchers have investigated RMET performance in non-treatment seeking individuals (Mitchell et al., 2016), and during the second (Thoma et al., 2013), and third weeks (Maurage et al., 2011) of detoxification, but not during the early stages. One study showed that patients undergoing detoxification have significantly lower RMET scores compared to healthy controls (Frileux et al., 2020). Moreover, statistical methods that can support both the presence and absence of effects (e.g., Bayesian hypothesis testing; Quintana and Williams, 2018) have yet to be applied in this field. Thus, the aim of this study was to investigate whether intranasal oxytocin influenced social emotional recognition in patients during the first three days of acute alcohol detoxification using a combination of frequentist and Bayesian inference approaches.

2. Material and methods

2.1. Study design

This investigation describes the analysis of a secondary outcome measure from a double blind, randomized placebo-controlled trial on intranasal oxytocin in alcohol withdrawal, including 39 patients admitted for alcohol detoxification at the Blue Cross Lade Addiction Treatment Centre (LBS) in Trondheim, Norway (Melby et al., 2019). The study was approved by the Regional Committee for Medical and Health Research in Central Norway (No. 2016/45) and the Norwegian Medicines Agency (No. 2015-004463-37) and was registered in clinicaltrials.gov (identifier NCT02903251). Eligible subjects were 18–65 years of age who lived in Trøndelag county, Norway. Further inclusion criteria are presented in detail elsewhere (Melby et al., 2019). To be included in the study, the average alcohol consumption was required to be in the range of 8–30 standard drinks (one standard drink = 12.8 g alcohol) per day for at least two weeks prior to enrolment in the study, which was assessed using the Timeline Follow-Back (TLFB) (Sobell et al., 1988). The primary outcome of the study was to evaluate the effects of oxytocin administration on benzodiazepine use during alcohol withdrawal, which we previously reported (Melby et al., 2019).

2.2. Intranasal oxytocin intervention

Patients were included in the study at the day of admission to the treatment centre. Written informed consent was obtained from all eligible patients fulfilling the inclusion criteria. If subjects were visibly intoxicated or experienced moderate withdrawal at admission, the informed consent procedure was repeated the following day. An assessment with Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) was performed immediately after admission. Pharmacological treatment following standard practice at the ward was given at CIWA-Ar scores of 10 or above (Melby et al., 2019), before commencing any further study procedures.

Oxytocin nasal spray (Syntocinon; Alfasigma S.p.A., Bologna, Italy) and placebo were decanted into identical 10 ml pump-actuated nasal spray containers. The placebo spray contained identical constituents as the Syntocinon spray, except for the active ingredient. Randomization to oxytocin or placebo was performed using a web-based randomization system. Six nasal spray puffs were administered (containing a total dose of 24 IU oxytocin or placebo) in interchanging nostrils with 15-s intervals twice daily for three days at 9 am and 6 pm. The use of nasal spray devices was based on the recommendations for standardization of the use of intranasal oxytocin in clinical trials (Guastella et al., 2013) and adapted to fit the routines at the ward. Study nurses monitored self-administration at the ward. The RMET was split into two parts to reduce any practice effects. On day 2, patients completed the first 18 RMET items with test start approximately 40 min after nasal spray administration whereas the last 18 RMET items were completed approximately 40 min after nasal spray administration on day 3.

2.3. Theory of mind assessment

The Norwegian version of the thirty-six item RMET was used to evaluate theory of mind performance (Baron-Cohen et al., 2001). Stimuli were photographs of the human eye region presented on a black background in the center, surrounded by four labels with mental state descriptions in the corners. The patients were instructed to select the description they thought best matched what the person in the photograph was thinking or feeling. The primary endpoint was any difference in the number of correct answers.

2.4. Statistical analysis

As this study was embedded in a randomized clinical trial on the effect of oxytocin on benzodiazepine use during alcohol withdrawal the power calculation was based on that endpoint (Melby et al., 2019). Statistical analyses were performed with R and JASP version 0.14.1 (JASP, n.d). Patients, clinical personnel, researchers and statisticians were blinded to group allocation until the statistical calculations were finished.

Performance on the RMET on day 2 and day 3 between oxytocin and placebo groups were compared using Welch's *t*-test. To assess the relative evidence for an alternative and null hypothesis, we performed Bayesian hypothesis testing (Quintana and Williams, 2018). A Bayes factor value >3 was considered to be moderate evidence for one model relative to the other. An "Oosterwijk" informed prior distribution (a t-distribution centred at 0.35, with a scale of 0.102 and 3 degrees of freedom) was used, as this represents the small-to-medium effects typically observed in the biobehavioral sciences. In addition, we fitted a linear regression model with RMET performance as the outcome, and treatment group, oxazepam doses during detoxification, alcohol intake, and the interaction of alcohol intake and treatment, as predictors. A Bayesian regression model with the same parameters was also fit with an r scale of 0.354 used for the prior distribution scale. A Bayes factor value >3 was considered to be moderate relative evidence for models. In addition to the preregistered analysis of the total RMET scores, the same analyses were performed on subscores that split RMET items by difficulty (easy/difficult Baron-Cohen et al., 2001) and emotion category (positive/negative/neutral Harkness et al, 2005) for both day 2 and day 3 (i.e., ten tests), which was not pre-registered. The statistical significance threshold was adjusted to $p = 0.005$ using a Bonferroni correction.

3. Results

Thirty-seven out of the 39 patients included in the main study (18 in the oxytocin and 19 in the placebo group) completed the RMET on day 2 and 3 (Supplementary Fig. 1). Baseline characteristics are presented in Table 1. On day 2, the difference in RMET performance was not statistically significant (a mean score of 11.56 in the oxytocin group vs. 10.95 in the placebo group; difference = 0.61, 95 % CI [−0.63, 1.84], t(35.70) = 0.99, $p = 0.327$; Cohen's d = 0.33, 95 % CI [−0.33, 0.99]; Fig. 1A). Similarly, the difference of RMET performance on day 3 was not statistically significant (a mean score of 11.95 in the oxytocin group vs. 11.37 in the placebo group; difference = 0.58, 95 % CI [−1.21, 2.37], t(31.26) = 0.66, $p = 0.514$; Cohen's d = 0.24, 95 % CI [−0.47, 0.94];

Fig. 1B). Bayesian *t*-tests revealed that there was 3.94 times more evidence for a null model relative to an alternative model for RMET differences at day 2 and 3.14 times more evidence for a null model relative to an alternative model for RMET differences at day 3 (Fig. 1C and D). There was no significant difference in RMET scores when combining scores from day 2 and day 3 (a mean score of 23.61 in the oxytocin group vs. 22.16 in the placebo group; difference = −1.45, 95 % CI [−4.24, 1.33], t(33.01) = −1.06, $p = 0.3$; Cohen's d = −0.35, 95 % CI [−1, 0.3]. A Bayesian *t*-test revealed that there was 4.09 times more evidence for a null model relative to an alternative model in combined RMET performance. As requested by a reviewer, ten Welch's tests were performed to evaluate group differences on RMET subscore performance on both day 2 and day 3 (Supplementary Table 1). While none of these tests were statistically significant using an adjusted threshold of $p = 0.005$, negative emotion RMET subscale scores on day 3 were significantly better after oxytocin treatment compared to placebo when using a conventional p value threshold of 0.05 ($p = 0.038$, Cohen's $d = 0.7$, $BF_{10} = 5.21$). One Bayesian *t*-test revealed at least moderate evidence for a null model relative to an alternative model (Positive emotion subscale on day 3; $BF_{01} = 3.17$). The eight remaining Bayesian t-tests delivered inconclusive results, which is indicative of insensitive data for these subscore tests (Supplementary Table 1).

Diagnostic tests revealed sufficient quality for the model predicting RMET performance by treatment group, alcohol intake, and their interaction, for day 2 and day 3. The RMET day 2 model was statistically significant [F(3,34) = 2.9, $p = 0.049$], accounting for 13.3 % of the variance in RMET performance. Alcohol use was a statistically significant predictor of RMET performance ($t = -2.2$, $p = 0.032$), however treatment group ($t = -0.84$, $p = 0.41$), or the treatment group x alcohol use interaction ($t = 0.4$, $p = 0.69$) coefficients were not statistically significant. The relationship between RMET performance on day 2 and alcohol use, grouped by treatment condition, is presented in Fig. 2A. In terms of Bayesian linear regression, the full model ($BF_{01} = 1.93$), main effects model ($BF_{01} = 1.06$), and group only model ($BF_{01} = 2.40$) demonstrated anecdotal evidence for the null hypothesis. The alcohol only model demonstrated anecdotal evidence for the alternative model ($BF_{10} = 1.88$). Results for RMET subscores for day 2 are presented in Supplementary Tables 2–6).

The RMET day 3 model was not statistically significant [F (3,34) = 1.8, $p = 0.16$], with the full model accounting for 6.3 % of the variance in RMET performance. For the individual coefficients, alcohol use ($t = -1.74$, $p = 0.09$), treatment group ($t = -0.46$, $p = 0.65$), and the treatment group x alcohol use interaction ($t = 1.3$, $p = 0.9$) coefficients were not statistically significant. The relationship between RMET performance on day 3 and alcohol use, grouped by treatment condition, is presented in Fig. 2B. In terms of Bayesian linear regression, the full model ($BF_{01} = 5.44$) demonstrated moderate evidence for the null hypothesis, relative to the alternative hypothesis. The main effects ($BF_{01} = 2.2$) and treatment group only ($BF_{10} = 2.71$) models demonstrated anecdotal evidence for the null hypothesis. The models assessing alcohol use demonstrated anecdotal evidence for the alternative model ($BF_{10} = 1.1$). Results for RMET subscores for day 3 are presented in Supplementary Tables 7–11. There were no significant differences between the groups on day 2 and day 3 when adding oxazepam dosage as a covariate (data not shown).

As requested by a reviewer, exploratory *t*-tests were performed to analyse the effects of alcohol consumption levels (based on average units of alcohol consumed before submission) on oxytocin treatment response indexed by RMET performance on day 2 and day 3. Individuals in the higher consumption group consumed an average of 20 units or more of alcohol daily before admission (range = 20–33 units) whereas individuals in the lower consumption group consumed <20 units of alcohol daily before admission (range = 7–19 units). Thus, four frequentist and Bayesian t-tests were performed. In the higher consumption group, oxytocin administration improved total RMET score performance on day 2 (a mean score of 10.67 in the oxytocin group vs. 9.00 in the placebo group; difference = −1.67, 95 % CI [0.30, 3.03], t(7.61) = 2.84, $p = 0.023$; Cohen's d = 2.06, 95 % CI [0.27, 3.76]). However, this effect did not survive Bonferroni correction for four tests (i.e., an adjusted critical alpha level of 0.0125). There was no significant difference in scores in the higher alcohol consumption subgroup on day 3 or in the lower alcohol consumption subgroup on either day 2 or day 3 (Supplementary Table 12).

Table 1
Baseline characteristics and clinical data of 39 patients with alcohol withdrawal syndrome randomized to treatment with either oxytocin nasal spray or placebo.

	Oxytocin group (n = 19)	Placebo group (n = 20)	*P* value
Gender (males/females)	12/7	16/4	0.243
Age (years), mean ± SD	48.4 ± 11.4	46.7 ± 9.7	0.603
Marital status (single/cohabiting)	13/6	14/6	0.915
Self-reported daily alcohol intake during the last 14 days (standard alcohol units[a]), mean ± SD	16.1 ± 7.2	15.0 ± 6.4	0.616

SD = standard deviation.
[a] One standard alcohol unit corresponds to 12.8 g ethanol.

4. Discussion

The main finding in this study was that oxytocin administration during alcohol withdrawal in alcohol-dependent patients did not improve social cognition performance as indexed by performance on the RMET. Moreover, alcohol use before detoxification significantly predicted RMET performance on day 2, but not on day 3 of withdrawal. While there was some evidence that oxytocin treatment may improve theory of mind ability in some contexts (i.e., only when presented with negative emotions or in participants who consumed 20 or more units of alcohol daily on average), it is important to note that these subscore and subgroup analyses were exploratory (i.e., not preregistered) and did not survive critical alpha correction for multiple tests. However, these exploratory results can help shape hypotheses for future research. These findings support another study on patients on day 2 of detoxification, where the patient group had significantly lower RMET scores on all items compared to the healthy control group, though the healthy controls had a lower mean age, higher level of education and were all employed (Frileux et al., 2020). Other studies have investigated RMET performance later in the detoxification process, such as day 8 of detoxification (Thoma et al., 2013), during the third week of detoxification (Maurage et al., 2011), after at least three weeks after detoxification (Nandrino et al., 2014) and after about six weeks of abstinence (Kopera et al., 2018). Three of these studies (Maurage et al., 2011; Nandrino et al., 2014; Thoma et al., 2013) showed that alcohol dependent patients had impaired social cognition with lower mean RMET scores than the healthy controls on the total score. Yet, no significant differences were seen in a study with 92 alcohol dependent patients and healthy controls (Kopera et al., 2018). The authors of the latter study suggest that gender, subgroups of alcohol dependent patients, or comorbid depression might explain the different outcomes between studies. Indeed, this is consistent with the present study, which indicates that oxytocin might be more effective for the subgroup of alcohol dependent individuals that consume especially higher levels of alcohol. Prior research of oxytocin in healthy subjects and patients with mental disorders has also shown conflicting results. For example, oxytocin has been reported to increase RMET scores in neurotypical men (Domes et al., 2007), yet these findings could not be replicated (Radke and de Bruijn, 2015). We did not investigate differences in early attachment and childhood trauma in the treatment groups, which might influence the effects of oxytocin (Mitchell et al., 2016). Prior work has reported worse RMET performance for positive and negative items, but not neutral items, in alcohol dependent individuals compared to controls

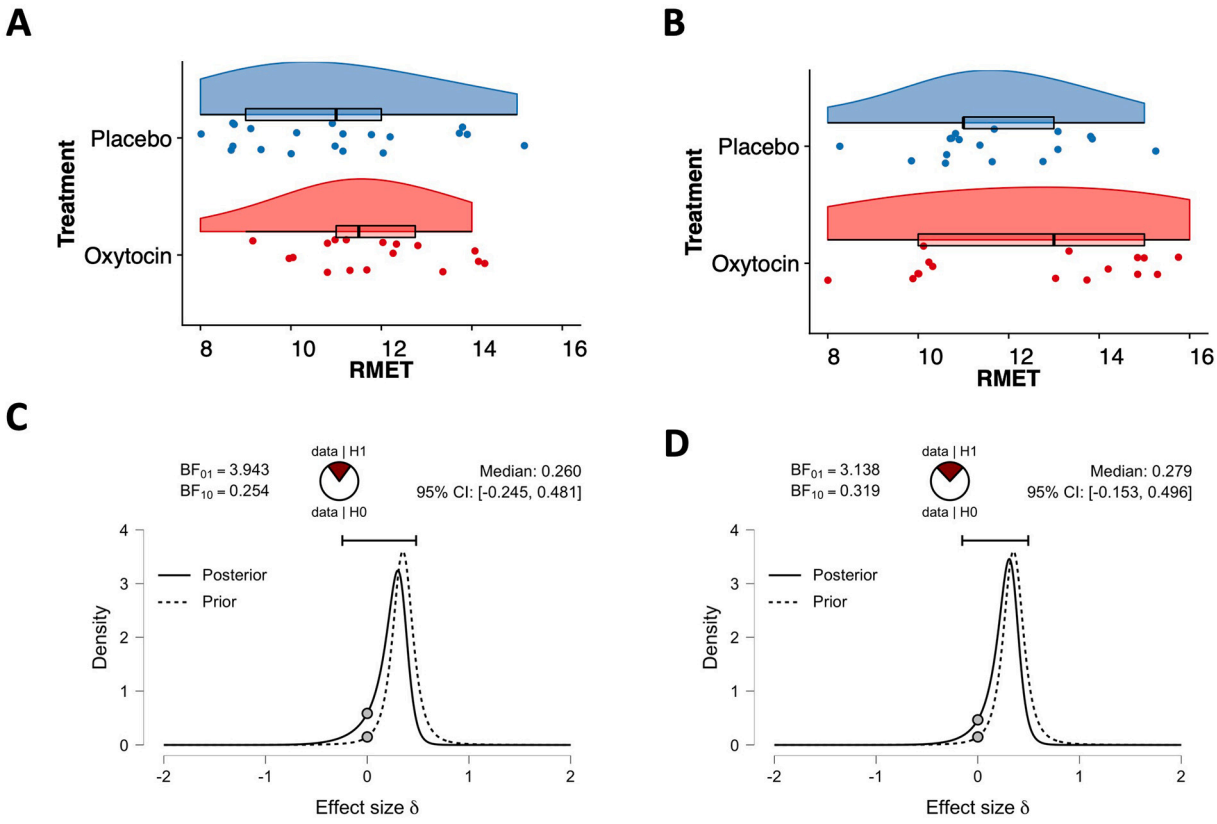

Fig. 1. RMET scores in patients with alcohol dependence undergoing treatment with oxytocin or placebo. Raincloud plots illustrate the number of correct answers on RMET performance on day 2 (A) and day 3 (B) during acute alcohol withdrawal in the oxytocin and placebo treatment groups. These show the data distribution (i.e., a split-half violin plot), the raw jittered data points, and a boxplot illustrating the median and interquartile range. Plots are also shown illustrating the prior and posterior distributions for the Bayesian independent samples *t*-test for RMET performance on day 2 (C) and day 3 (D).

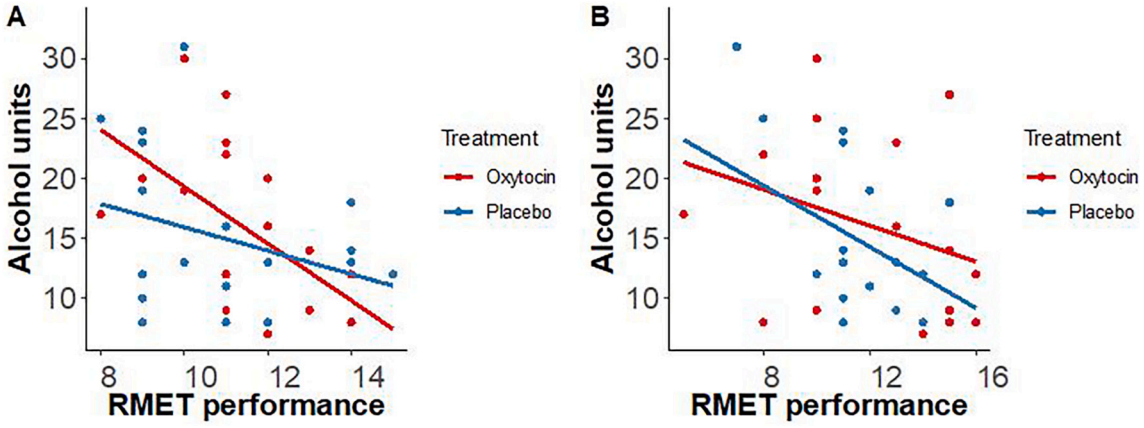

Fig. 2. The relationship between alcohol use (average alcohol consumption per day) and RMET performance in patients with alcohol dependence undergoing treatment. Alcohol use was assessed using the Timeline Follow Back method. Data is shown for RMET performance during day 2 (A) and day 3 (B) of treatment with either oxytocin or placebo.

(Maurage et al., 2011). While exploratory analyses revealed a statistically significant difference in performance on the negative items at day 2, this did not survive correction for multiple tests.

The sample size in the present study and analysis was relatively small, particularly for the reliable detection of RMET subscore effects, which is due to the study being designed to detect other outcomes. Larger samples in future research will facilitate the reliable detection for a wider range of effect sizes. Moreover, dividing the RMET in two parts, with the first 18 items on day 2 and the last 18 on day 3, to keep the test load as low as possible during detoxification and to help prevent practice effects, may have influenced the operationalization of social cognition, though split half reliability has shown moderate to good internal consistency, and has been used in other studies (Burke et al., 2016; Eddy and Hansen, 2020). Another consideration is that patients were receiving benzodiazepines during the study to alleviate withdrawal symptoms and there is a potential risk that benzodiazepine intake may affect RMET scores. This was also a limitation in the study by Frileux et al. (2020), where the patient group completed the RMET when the withdrawal symptoms measured by the CIWA-Ar were absent due to benzodiazepine treatment (Frileux et al., 2020). However, adding benzodiazepine intake

as a covariate in the analyses, which can be used as a proxy of withdrawal severity, did not appreciably influence the results in our study. In terms of study design, another limitation is that without a comparison group that was not alcohol dependent it is also not clear whether a failure to detect clear effects of oxytocin is due to a lack of reduction in RMET performance in the alcohol dependent participants (i.e., ceiling effects). However, evidence that increased alcohol consumption was associated with decreased RMET scores ameliorates this issue to a small degree. Finally, we did not collect any repeated measures of cognitive or affective state, so it is unclear whether oxytocin may have had other effects beyond social cognition.

As we did not measure urine or plasma oxytocin levels, there is a chance that the intranasal oxytocin does not reach the CNS (Leng and Ludwig, 2016; Walum et al., 2016), though a more recent study has shown effects on eye and amygdala activity after intranasal oxytocin administration (Quintana et al., 2019).

Altogether, our study provided moderate evidence that 2 or 3 days of oxytocin treatment during alcohol withdrawal does not influence RMET performance although there is some preliminary evidence to suggest oxytocin might improve performance on the RMET negative item subscale and that individuals who consume high levels of alcohol could be more responsive to oxytocin treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2022.105268.

Funding

This work was supported by the joint research council between St. Olav University Hospital and the Faculty of Medicine and Health Sciences of Norwegian University of Science and Technology – NTNU, the Research Departments of St. Olav University Hospital, and the Research Council of Norway (324783).

Declaration of competing interest

None.

Data availability

Data will be made available on request.

References

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241–251.

Burke, T., Pinto-Grau, M., Lonergan, K., Elamin, M., Bede, P., Costello, E., Hardiman, O., Pender, N., 2016. Measurement of social cognition in amyotrophic lateral sclerosis: a population based study. PLoS One 11, e0160850.

Domes, G., Heinrichs, M., Glascher, J., Buchel, C., Braus, D.F., Herpertz, S.C., 2007. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol. Psychiatry 62, 1187–1190.

Eddy, C.M., Hansen, P.C., 2020. Predictors of performance on the Reading the Mind in the Eyes test. PLoS One 15, e0235529.

Foisy, M.L., Kornreich, C., Fobe, A., D'Hondt, L., Pelc, I., Hanak, C., Verbanck, P., Philippot, P., 2007. Impaired emotional facial expression recognition in alcohol dependence: do these deficits persist with midterm abstinence? Alcohol. Clin. Exp. Res. 31, 404–410.

Frileux, S., Dubertret, C., Le Strat, Y., 2020. Short-term impact of alcohol detoxification on facial emotions recognition. Encephale 46, 319–325.

Guastella, A.J., Hickie, I.B., McGuinness, M.M., Otis, M., Woods, E.A., Disinger, H.M., Chan, H.K., Chen, T.F., Banati, R.B., 2013. Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. Psychoneuroendocrinology 38, 612–625.

JASP (Version 0.14.1)[Computer software].

Harkness, et al., 2005. Enhanced accuracy of mental state decoding in dysphoric college students. Cogn. Emot. 19 (7) https://doi.org/10.1080/02699930541000110.

King, C.E., Gano, A., Becker, H.C., 1736. The role of oxytocin in alcohol and drug abuse. Brain Res. 2020, 146761.

Kopera, M., Trucco, E.M., Jakubczyk, A., Suszek, H., Michalska, A., Majewska, A., Szejko, N., Loczewska, A., Krasowska, A., Klimkiewicz, A., Brower, K.J., Zucker, R. A., Wojnar, M., 2018. Interpersonal and intrapersonal emotional processes in individuals treated for alcohol use disorder and non-addicted healthy individuals. Addict. Behav. 79, 8–13.

Leng, G., Ludwig, M., 2016. Intranasal oxytocin: myths and delusions. Biol. Psychiatry 79, 243–250.

Marlatt, G.A., 1996. Taxonomy of high-risk situations for alcohol relapse: evolution and development of a cognitive-behavioral model. Addiction 91 (Suppl), S37–S49.

Maurage, P., Grynberg, D., Noel, X., Joassin, F., Hanak, C., Verbanck, P., Luminet, O., de Timary, P., Campanella, S., Philippot, P., 2011. The "Reading the mind in the eyes" test as a new way to explore complex emotions decoding in alcohol dependence. Psychiatry Res. 190, 375–378.

Melby, K., Grawe, R.W., Aamo, T.O., Salvesen, O., Spigset, O., 2019. Effect of intranasal oxytocin on alcohol withdrawal syndrome: a randomized placebo-controlled double-blind clinical trial. Drug Alcohol Depend. 197, 95–101.

Mitchell, J.M., Arcuni, P.A., Weinstein, D., Woolley, J.D., 2016. Intranasal oxytocin selectively modulates social perception, craving, and approach behavior in subjects with alcohol use disorder. J. Addict. Med. 10, 182–189.

Nandrino, J.L., Gandolphe, M.C., Alexandre, C., Kmiecik, E., Yguel, J., Urso, L., 2014. Cognitive and affective theory of mind abilities in alcohol-dependent patients: the role of autobiographical memory. Drug Alcohol Depend. 143, 65–73.

Onuoha, R.C., Quintana, D.S., Lyvers, M., Guastella, A.J., 2016. A meta-analysis of theory of mind in alcohol use disorders. Alcohol Alcohol. 51, 410–415.

Quintana, D.S., Williams, D.R., 2018. Bayesian alternatives for common null-hypothesis significance tests in psychiatry: a non-technical guide using JASP. BMC Psychiatry 18, 178.

Quintana, D.S., Westlye, L.T., Alnaes, D., Kaufmann, T., Mahmoud, R.A., Smerud, K.T., Djupesland, P.G., Andreassen, O.A., 2019. Low-dose intranasal oxytocin delivered with breath powered device modulates pupil diameter and amygdala activity: a randomized controlled pupillometry and fMRI study. Neuropsychopharmacology 44, 306–313.

Radke, S., de Bruijn, E.R., 2015. Does oxytocin affect mind-reading? A replication study. Psychoneuroendocrinology 60, 75–81.

Sobell, L.C., Sobell, M.B., Leo, G.I., Cancilla, A., 1988. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br. J. Addict. 83, 393–402.

Thoma, P., Winter, N., Juckel, G., Roser, P., 2013. Mental state decoding and mental state reasoning in recently detoxified alcohol-dependent individuals. Psychiatry Res. 205, 232–240.

Walum, H., Waldman, I.D., Young, L.J., 2016. Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. Biol. Psychiatry 79, 251–257.