



Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia[☆]

David Feifel^{*}, Kai MacDonald, Patrice Cobb, Arpi Minassian

Department of Psychiatry, University of California, San Diego, United States

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ABSTRACT

Introduction: Cognitive deficits are a prominent, disabling component of schizophrenia and current pharmacological treatments have demonstrated limited efficacy in their amelioration. Oxytocin – though it has shown promise as a novel antipsychotic in multiple clinical trials – has as-yet poorly characterized effects on cognition, with some evidence indicating an amnesic profile.

Method: As part of a previously reported trial of chronic adjunctive oxytocin in schizophrenia, we measured its effect on two cognitive tests: the CVLT (California Verbal Learning Test) and the LNS (Letter Number Sequence). Tests were performed at baseline and after 3 weeks of treatment.

Results: We found no evidence for an amnesic effect and, in fact, significantly better performance with oxytocin on several subtests of the CVLT; namely total Recall trials 1–5 ($p = 0.027$), short delayed free recall ($p = 0.032$) and total recall discrimination ($p = 0.020$). In contrast we found no difference between placebo and oxytocin on LNS performance.

Conclusions: This is the first report we are aware of documenting a beneficial effect of oxytocin on cognition in schizophrenia. Though from a small sample ($n = 15$), these data both offset past concerns about oxytocin's amnesic effects, and may auger another potential benefit in addition to the already-demonstrated salutary effects on other components of the illness.

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1. Introduction

Impairments in cognitive and executive functions are a significant component of schizophrenia. These deficits, which include problems with attention, abstract reasoning, visual, working and verbal memory (Van Snellenberg, 2009), are – at best – only partially ameliorated with current antipsychotic medications (O'Grada and Dinan, 2007). This shortcoming is notable, as these impairments often predict patient's level of dysfunction (O'Grada and Dinan, 2007). Though there have been efforts to develop psychopharmacologic treatments to address this cluster of symptoms (Kane and Correll, 2010), no current medications have demonstrated decisive functional gains.

Building on animal models demonstrating oxytocin's antipsychotic potential (Feifel and Reza, 1999; Caldwell et al., 2009; Feifel et al., 2012), recent clinical trials have shown oxytocin is a promising treatment for schizophrenia (Feifel et al., 2010; Pedersen et al., 2011). Specifically, our group demonstrated that 3 weeks of twice-daily intranasal oxytocin (40 IU) added to antipsychotic medication significantly improved both positive and negative symptom domains of the illness (Feifel et al., 2010). Cognizant of the fact that amnesic effects

have been reported in humans treated with oxytocin (Ferrier et al., 1980; Fehm-Wolfsdorf et al., 1984; Bruins et al., 1992), we included two memory tasks as secondary measures in our study, the California Verbal Learning Test (CVLT II) (Delis et al., 2000) and Letter Number Sequencing (LNS) task (Wechsler, 1997). We have previously reported the main outcome measures of our clinical trial (PANSS and CGI score), and we now report the results of these memory tests.

2. Methods

2.1. Subjects

We conducted a double-blinded, placebo-controlled crossover study comparing oxytocin to placebo. The details of this study design are reported elsewhere (Feifel et al., 2010) but briefly, subjects with a SCID-confirmed DSM-IV diagnosis of schizophrenia were enrolled. At enrollment, subjects had to be on a stable dose of at least 1 approved antipsychotic medication for four weeks, have a minimum positive and negative syndrome scale (PANSS) score of at least 55, and at least a score of 4 (moderate) on item 6 (suspiciousness/persecution).

2.2. Dosing

Subjects maintained their pre-study antipsychotic medication regimen and received 3-weeks of daily intranasal oxytocin (20 IU twice

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^{*} Corresponding author at: Department of Psychiatry, University of California, San Diego, 200 West Arbor Drive, San Diego, MC8218, 92103, United States.

E-mail address: dfeifel@ucsd.edu (D. Feifel).

daily for 1 week, then 40 IU twice daily thereafter) (Syntocin, Novartis, Basel Switzerland) and 3-weeks of daily intranasal placebo. Order of treatment (placebo–oxytocin or oxytocin–placebo) was randomly assigned. This study was approved by the UCSD Institutional Review Board and written informed consent was obtained from all subjects before any study procedures were performed.

Subjects had weekly symptom rating scales and safety assessments; these findings have previously been reported (Feifel et al., 2010). Patients performed CVLT and LNS at baseline and again at the last visit (week 3) of each treatment period.

2.3. Cognitive measures

The CVLT-II is a commonly-used test of new learning and declarative verbal memory (Delis et al., 2000) (see supplement for test details). In brief, subjects read a list of 16 words over 5 trials, and engage in a variety of recall tasks, including free recall, recall after an interference list is read, recall after different amounts of elapsed time (i.e. short and long delay) and discriminating between words from different lists. Each task generates a different subscore.

The LNS is a component of the WAIS-III (Wechsler, 1997) and is used to measure working memory. In each trial of the LNS, a list of letters and numbers are read in a mixed order to participants; participants are asked to recall first the digits and then the letters in the order they were presented. Length of the list ranges from 2 to 8; each length is tested three times. Scores are calculated by totaling the correct responses for each length.

2.4. Statistical analyses

Raw scores from the CVLT-II and LNS were subjected to analysis. Our primary outcome measurement was the total recall across trials 1 to 5, as it is the core measure of the memory and learning in the CVLT. Other recall measures analyzed as secondary measures were: short-delay free recall, long-delay free recall, total recall discriminability and total recognition discriminability. The LNS generates a single score.

For each CVLT measure and for LNS data, separate repeated measures ANOVAs were performed with drug as within subject factor and treatment sequence as a between subject factor. The later factor was included to explore the influence on drug sequence assignments on drug effects. If there was a significant interaction effect (i.e. treatment sequence X drug) then drug effects from subjects who received placebo–oxytocin and subjects who received oxytocin–placebo were compared separately using paired *t*-tests. If there was a significant main effect of drug but not a significant interaction effect, then data were collapsed across treatment sequence and placebo was compared to oxytocin for all subjects using a single paired *t*-test. Effect size (ES) for each oxytocin–placebo difference was also calculated using the Cohen's *d* method.

In order to determine the influence of practice effects, the outcomes of the scores from the placebo–oxytocin group and oxytocin–placebo group were calculated separately and visually inspected.

3. Results

3.1. Participants

20 subjects enrolled, and 15 (12 males, 3 females) completed both treatment arms (Table 1). Average age was 48.0 $\pm$ 8.9 years, average time ill 25.8 $\pm$ 14.5 years. For more demographic details see Feifel et al. (2010).

Table 1
Subjects demographics.

	N	%
Gender		
Male	12	80%
Female	3	20%
Race		
Caucasian	4	26.70%
Black	8	53.30%
Other	3	20%
Initial treatment		
Oxytocin	6	40%
Placebo	9	60%
Age (STD)	48	(8.9)
Average years of education (STD)	12.7	(2.3)
Average PPVT (STD)	91.7	(21.6)
Average years ill (STD)	25.8	(14.5)

3.2. Cognitive tests

None of the ANOVAs performed on the CVLT measures revealed a significant main effect of treatment sequence or a significant interaction between drug X treatment sequence (Fig. 1). There were significant effects of drug for total recall trials 1–5 ($F(1,13) = 4.97$, $p < 0.05$), short delayed free recall ($F(1,13) = 4.61$, $p < 0.05$), and total recall discrimination ($F(1,13) = p < 0.5$) but not for long delay free recall, or total recognition discriminability. Post-hoc paired *t*-test performed on the measures that produced a significant drug effect revealed that oxytocin scores were significantly higher than placebo scores for total recall trials 1–5 ($t(14) = 2.47$, $p = 0.027$; $ES = 0.64$), for short delayed free recall ($t(14) = 2.38$, $p = 0.032$; $ES = 0.61$) and total recall discrimination ($t(1,14) = 2.63$, $p = 0.020$; $ES = 0.68$) but not for long delay free recall ($ES = 0.08$), or total recognition discriminability ($ES = 0.37$). We conducted a secondary analysis of trial 1 recall only as well as semantic and serial clustering but found no differences between oxytocin and placebo on these measures.

ANOVA performed on LNS scores revealed no significant effect of drug or treatment sequence and no significant drug X treatment sequence interaction (Fig. 1).

4. Discussion

In this secondary analysis, we found that 3-weeks of intranasal oxytocin improved performance on several CVLT measures but not LNS. Although several studies have shown that a single dose of intranasal oxytocin improves non-verbal social memory (Striepens et al., 2011 for review), to our knowledge the improvement we report on the CVLT is the first evidence of beneficial effects of oxytocin on verbal memory. In fact, all four previous reports of single-dose oxytocin testing verbal recall found that it worsened after treatment (Ferrier et al., 1980; Fehm-Wolfsdorf et al., 1984; Bruins et al., 1992; Heinrichs et al., 2004), and a recent report in normal subjects found amnesic effects of oxytocin for both social and nonsocial objects (Herzmann et al., 2012). Regarding longer-term effects of OT, a single case report describing the effects of four weeks of treatment with intranasal oxytocin describes a patient with obsessive compulsive disorder who developed significant amnesia (though without specific mention of verbal memory) (Ansseau et al., 1987).

Thus, the current finding of enhanced CVLT performance was surprising, and raises interesting questions regarding whether this mnemonic effect is specific to schizophrenia patients or extends to other memory-related disorders and even healthy subjects. Deficits in verbal memory are one of the most consistent cognitive deficits in schizophrenia, and as such, have been proposed as an endophenotype of the disorder.

Notably, the observed benefits of oxytocin were stronger for short-term recall than long-term recall. Different neural circuitry

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