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The effects of oxytocin on social cognition and behaviour in frontotemporal dementia

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Patients with behavioural variant frontotemporal dementia demonstrate abnormalities in behaviour and social cognition, including deficits in emotion recognition. Recent studies suggest that the neuropeptide oxytocin is an important mediator of social behaviour, enhancing prosocial behaviours and some aspects of emotion recognition across species. The objective of this study was to assess the effects of a single dose of intranasal oxytocin on neuropsychiatric behaviours and emotion processing in patients with behavioural variant frontotemporal dementia. In a double-blind, placebo-controlled, randomized cross-over design, 20 patients with behavioural variant frontotemporal dementia received one dose of 24 IU of intranasal oxytocin or placebo and then completed emotion recognition tasks known to be affected by frontotemporal dementia and by oxytocin. Caregivers completed validated behavioural ratings at 8 h and 1 week following drug administrations. A significant improvement in scores on the Neuropsychiatric Inventory was observed on the evening of oxytocin administration compared with placebo and compared with baseline ratings. Oxytocin was also associated with reduced recognition of angry facial expressions by patients with behavioural variant frontotemporal dementia. Together these findings suggest that oxytocin is a potentially promising, novel symptomatic treatment candidate for patients with behavioural variant frontotemporal dementia and that further study of this neuropeptide in frontotemporal dementia is warranted.

Keywords: frontotemporal dementia; oxytocin; facial expressions; theory of mind
Abbreviations: FTD = frontotemporal dementia

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Introduction

Frontotemporal dementia (FTD) is a devastating, progressive neurodegenerative disease for which there is presently no available cure, and only a few symptomatic treatments that are marginally effective. Early in the course of the disease, patients with the behavioural variant of FTD develop striking deficits in fundamental components of social and emotional behaviour including emotional blunting, indifference, callousness and loss of empathy for even their closest family members (Kertesz *et al*., 2000; Perry *et al*., 2001; Rankin *et al*., 2003, 2006). To date, there are no curative or disease-modifying treatments for FTD, nor any approved treatments for symptoms of FTD (Boxer and Boeve, 2007). As FTD is increasingly recognized and diagnosed, the lack of effective treatments for the most troubling symptoms and behaviours in this disorder is a critical unmet need.

Diagnostic criteria and clinical rating scales for the behavioural variant of FTD highlight a progressive decline in interpersonal behaviour and emotional blunting (Neary *et al*., 1998; Rascovsky *et al*., 2010). More recent work has begun to elucidate the components of social cognition thought to be necessary for appropriate social behaviour in patients with established diagnosis of FTD. One such fundamental building block is facial expression processing. Facial expressions communicate information critical for appropriate social behaviour (Blair, 2003). Deficits in facial expression recognition are associated with inappropriate and anti-social behaviours (Marsh *et al*., 2007, 2008). Patients with behavioural variant of FTD reliably show impaired recognition of negative facial expressions (e.g. fear, sadness) (Keane *et al*., 2002; Fernandez-Duque and Black, 2005). The neural regions implicated in facial expression processing are also thought to be involved in the experience of these emotions (Preston and de Waal, 2002; Carr *et al*., 2003; Wicker *et al*., 2003). Thus, deficits in expression processing not only indicate recognition deficits but may also provide a window into the internal emotional experience of patients. In addition to facial expression processing impairments, patients with behavioural variant FTD show deficits in auditory emotion recognition (Perry *et al*., 2001) and theory of mind processing (processing the thoughts and intentions of others) (Gregory *et al*., 2002). Deficits in these emotion recognition skills are thought to contribute to the deficits in empathy and inappropriate social behaviours in FTD (Gregory *et al*., 2002; Snowden *et al*., 2003; Lough *et al*., 2006).

A growing body of research on the neuropeptide oxytocin suggests it is an important mediator of social behaviour across species. Oxytocin is produced in the supraoptic and paraventricular nuclei of the hypothalamus and delivered to the pituitary for systemic release into circulation. Oxytocin is also delivered directly to regions of the CNS including afferent projections, and paracrine signalling of oxytocin receptors in regions including the amygdala, nucleus accumbens and prefrontal cortex (Wang *et al*., 1997; Smeltzer *et al*., 2006; Ross *et al*., 2009; Schorscher-Petcu *et al*., 2009; Goodson and Thompson, 2010). Oxytocin administration promotes prosocial maternal behaviours such as feeding, nest building and grooming of pups (Pedersen *et al*., 1982; Kendrick *et al*., 1987), while antagonism of oxytocin receptors decreases these behaviours (Champagne *et al*., 2001). In addition to the long-recognized role of oxytocin in pregnancy and lactation, injection of oxytocin into the amygdala in mammalian species reverses social deficits (Winslow and Insel, 2002).

Recent clinical studies in humans have investigated the effects of intranasal and intravenous oxytocin administration on social cognition and emotion processing in healthy adults and in patients with autism. In healthy adults, oxytocin administration is associated with increased cooperative behaviour as indexed by economic decision-making tasks (Kosfeld *et al*., 2005; Baumgartner *et al*., 2008). It is also associated with improved social cue processing such as improved theory of mind performance (Domes *et al*., 2007*b*), increased direction of eye gaze towards the eye region of human faces (Guastella *et al*., 2008*a*) and increased emotional empathy (Hurlemann *et al*., 2010). The effects of oxytocin on facial expression recognition have been less clear to date. A growing number of studies suggest it may enhance processing of positive expressions (Guastella *et al*., 2008*b*; Di Simplicio *et al*., 2009; Marsh *et al*., 2010). However, results are more conflicted with regard to negative emotions such as fear and anger; whereas some studies suggest that oxytocin administration improves the recognition of negative emotions (Savaskan *et al*., 2008; Fischer-Shofty *et al*., 2010), others show reduced identification of fearful and angry expressions (Di Simplicio *et al*., 2009; Evans *et al*., 2010). In patients with autism spectrum disorders, oxytocin administration improved trust and enhanced interactions with cooperative partners (Andari *et al*., 2010). Theory of mind task performance and affective speech comprehension are also enhanced by oxytocin administration in youths with autistic spectrum disorders (Hollander *et al*., 2007; Guastella *et al*., 2010). Together, the growing literature on the effects of oxytocin in humans suggests that the neuropeptide may enhance prosocial behaviours, as has been observed in other species. As a consequence, the upregulation of oxytocin-mediated mechanisms of empathy and prosocial behaviour may be a valuable symptomatic treatment approach for patients with FTD.

Oxytocin administered intranasally is rapidly absorbed from the nasal mucosa and the effects on the lactation response are observed within a few minutes. Detailed pharmacokinetics of the duration of action of intranasal oxytocin in the CNS and the CSF half-life are not yet available. However, human data from the closely related neuropeptide vasopressin indicate that significantly elevated levels likely occur within 10 min with peak levels within ~1 h, and an estimated duration of action of oxytocin in the CNS between 2–8 h (Born *et al*., 2002).

To assess the potential of oxytocin as a symptomatic treatment for the social and behavioural deficits in patients with FTD, we conducted a randomized, double-blind, placebo-controlled study examining the effects of a single dose of intranasal oxytocin on emotion recognition performance and behavioural variant of FTD-related behaviours. As no prior reported studies have evaluated the effects of oxytocin in FTD or other dementias, a single-dose design was selected for this first study to evaluate any unexpected negative effects on disease-related behaviours such as aggression, which have been observed in some animal studies (Bosch *et al*., 2005). We hypothesized that in patients with FTD, the associated atrophy in oxytocinergic projection regions

including medial prefrontal cortex and the amygdala would result in disruption of oxytocin circuits; furthermore, the augmentation of remaining neuronal connections may be achieved by administration of intranasal oxytocin. We predicted that oxytocin may enhance performance on emotion recognition tasks, particularly for positive emotions. We also predicted that oxytocin administration would result in improvements in caregiver reports of social functioning compared with placebo.

Materials and methods

Study design

This was a randomized, double-blind, placebo-controlled cross-over study of a one-time dose of 24 IU of intranasal oxytocin administered to patients with FTD. The primary outcome measure was emotion recognition, operationalized using a facial expression recognition task. Other measures of emotion processing and social cognition included an auditory emotion recognition task, and the Mind in the Eyes Theory of Mind task detailed below. Secondary outcome measures assessed whether a single dose of oxytocin improved FTD-related behaviours as indexed by caregiver reports ~8 h after treatment on the Neuropsychiatric Inventory (Cummings, 1997) and the Frontal Behavioural Inventory (Kertesz *et al*., 1997).

Participants

Eligible patients met the Neary *et al*. (1998) criteria for diagnosis of behavioural variant FTD and had MRI, CT or single-photon emission CT imaging consistent with the diagnosis. Thus, all participants met the new FTD consensus criteria (Rascovsky *et al*., 2010). All participants had emotional blunting features. Patients who initially presented with pure behavioural variant of FTD and later developed semantic deficits or non-fluent aphasia were included if language deficits were mild and comprehension of standard neuropsychological tasks was not impaired.

Exclusion criteria

Participants with comprehension deficits or language impairment that would preclude task completion were excluded from our study. Other exclusion criteria included history of stroke, tumour or other focal brain lesion, history of other neurological or psychiatric disorder that could account for the patient's symptoms, uncontrolled hypertension, current use of prostaglandins or use of any investigational or experimental drug or device within 60 days prior to screening. Caregiver ratings were obtained from the spouse or a close family member of the patients who could reflect on behavioural changes observed on the day of each experimental visit and 1 week later.

Procedures

A total of 20 patients with behavioural variant of FTD were enrolled in the study and all completed the screening and treatment visits. At the screening visit patients completed standard neuropsychological tests of memory, language and executive functions, and caregivers completed baseline behaviour ratings on the Neuropsychiatric Inventory and the entire Frontal Behavioural Inventory (Table 1). All participants were randomized to receive one dose of 24 IU of intranasal oxytocin (three puffs per nostril, 4 IU per puff; Syntocinon, Novartis) or placebo (saline mist). A dose of 24 IU was chosen based on prior studies reporting significant effects on emotion recognition tasks at this dose in healthy adults and in patients with autistic spectrum disorders (Kosfeld *et al*., 2005; Baumgartner *et al*., 2008; Guastella *et al*., 2008*a*; Rimmele *et al*., 2009; Hurlemann *et al*., 2010). Twenty minutes after the administration of the nasal solution, each patient attempted to complete a battery of validated emotion processing tasks (Facial Expression Recognition and Intensity, Vocal Affect and Mind in The Eyes). Task order was randomized across patients; for each individual patient, tasks were administered in the same order for their placebo and oxytocin treatment visits. Potential effects of oxytocin on behaviour were measured by caregiver ratings on the Neuropsychiatric Inventory and pre-selected sub-items of the Frontal Behavioural Inventory on the evening of the medication administration and 1 week later. Patients returned 2 weeks after the first treatment visit and received the alternate medication (placebo or oxytocin) followed by the same test battery and caregiver ratings of behaviour. Vital signs were recorded during each experimental visit prior to nasal solution administration and after completion of the emotion processing tasks. Adverse event and side-effect information was collected via follow-up telephone calls by a research nurse to caregivers on the evening of treatment visits and 1 week after each treatment visit.

Table 1 FTD patient demographics and standard neuropsychological test scores

	n	Mean ± SD
Age (years)	20	64.40 ± 7.40
Education (years)	20	12.85 ± 3.30
Illness duration (years)	20	4.96 ± 3.15
Mini Mental State Examination	20	23.40 ± 4.32
Prose—immediate recall (max possible = 21)	20	3.53 ± 3.25
Prose—delayed recall (max possible = 21)	20	2.83 ± 3.20
FAS letter fluency	20	17.10 ± 10.65
Semantic fluency (animals)	20	9.40 ± 5.71
Object naming/20	19	16.95 ± 4.09
Trail Making Test A (s)	19	53.05 ± 16.62
Trail Making Test B (s)	11	132.82 ± 78.55
National Adult Reading Test—number of errors/50	20	30.45 ± 13.76
Wisconsin Card Sorting Test/six categories	17	2.35 ± 2.40
Frontal Behaviour Inventory	20	37.68 ± 9.79
Neuropsychiatric Inventory—total domain score	20	32 ± 2.87

Prose recall was part of the River Mead testing package. Objects named were taken from the Western Aphasia Battery. One participant was not able to complete Trail Making Test A, and nine participants were not capable of completing Trail Making Test B.

Measures

Emotion recognition tasks

The Facial Expression Recognition and Intensity task was based on a task recently developed by colleagues at the University of Western Ontario for detecting emotion recognition deficits in neuropsychiatric patients. Participants were presented with an image of a facial expression (fearful, happy, sad or angry) from the standardized NimStim set

(Tottenham *et al*., 2009); images were morphed with Fantamorph software to display intensities of emotional expressions from 20% to 80% (Fig. 1A). While the target facial expression was displayed on the screen, participants were asked to select which emotional label (fear, happy, angry, sad or neutral) best fit the emotion expressed. The expression labels were then replaced by five exemplars of that actor displaying the emotion in varying degrees of intensity [0 (neutral), 20, 40, 60, 80 and 100%) (Fig. 1B). Patients were asked to select which picture was closest in intensity to the trial expression. The exact stimulus intensity presented for that trial (20–80%) was not included as a choice for that trial to prevent simple matching. Although none of the target expressions were displayed at 0 or 100%, these intensities were included in the list of exemplars to reduce the likelihood of ceiling and floor effects. The task consisted of 65 trials presented in random order.

For the vocal affect recognition task (Pell *et al.,* 2009), we administered a previously validated vocal affect recognition task to our patients following prior work demonstrating deficits in vocal affect recognition in FTD (Perry *et al*., 2001) and improvements in vocal affect processing following oxytocin administration to patients with autism (Hollander *et al*., 2007). The vocal affect recognition task involves the presentation of eight pseudo utterances (e.g. 'Someone migged the pazing') from each of seven emotional categories: anger, fear, sad, happy, disgust, neutral and surprise. A task involving pseudo-utterances was selected to reduce the influence of semantic content given potential semantic comprehension deficits in patients with FTD. Twenty-four of the utterances were categorized as high intensity and 24 were categorized as low intensity, with eight neutral utterances. The 56 auditory clips were played in random order. After each clip, the participant selected which emotion best described what was heard from the seven choices displayed on the computer screen. During each auditory clip and afterwards, the participants made their selection by pointing to their choice or by stating it aloud.

The Mind in the Eyes task (Baron-Cohen *et al.,* 2001*a*) is a validated measure of one form of Theory of Mind processing—the ability to judge a person's internal mental state based on the expression of his/her eye region. This task was selected because prior work using this task has demonstrated that patients with FTD have deficits in this form of theory of mind skills (Gregory *et al*., 2002). In addition, administration of oxytocin improves performance on this task in healthy adults and patients with autistic spectrum disorders (Domes *et al*., 2007*b*; Guastella *et al*., 2010). Participants were presented with images displaying the eye region of 28 actors in various mental states. The child version of the task was used to reduce language comprehension difficulty (Baron-Cohen *et al*., 2001*b*). Participants were asked to select the best choice from four emotional feelings displayed on the screen.

Behavioural ratings

The Neuropsychiatric Inventory (Cummings, 1997) measure is a caregiver response inventory reflecting on behaviour and personality change in the patient. Items included delusions, hallucinations, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep and appetite. Each item is rated on dimensions of behaviour frequency, severity and distress. Total scores were calculated by multiplying frequency by severity scores for each item and then summing the domain scores; higher scores indicate greater behaviour impairment (Connor *et al*., 2008).

The Frontal Behavioural Inventory is a caregiver response inventory reflecting on behavioural change in patients with FTD (Kertesz *et al*., 1997). Nine sub-items from this scale related to social cognition or repetitive behaviours were administered: apathy, indifference/emotional flatness, perseverations and obsessions, inappropriateness, excessive jocularity, impulsivity/poor judgement, irritability, aggression and hypersexuality. The highest possible total score on these sub-items was 27; higher scores were indicative of greater behaviour impairment.

Statistical analysis

Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS, Version 18). Repeated-measures ANOVAs with emotion, intensity and treatment as within-subject factors and treatment order as a between-subject factor were conducted on the percentage of correct responses for each of the emotion recognition tasks. Paired-sample *t*-tests were used to compare behavioural ratings from the evening following oxytocin administration versus placebo administration, and 1 week post-treatment on total scores from the Neuropsychiatric Inventory and on total scores on the Frontal Behavioural Inventory. There were no significant differences found in treatment order or interactions with treatment order on any of the measures; therefore, treatment order was excluded from the final analyses. Follow-up *t*-tests were conducted to interpret any interactions. All reported *t*-test *P*-values are two-tailed unless otherwise specified; *P*-values were not corrected for multiple comparisons. Due to sample size limitations, gender was not included as a factor in the primary analysis.

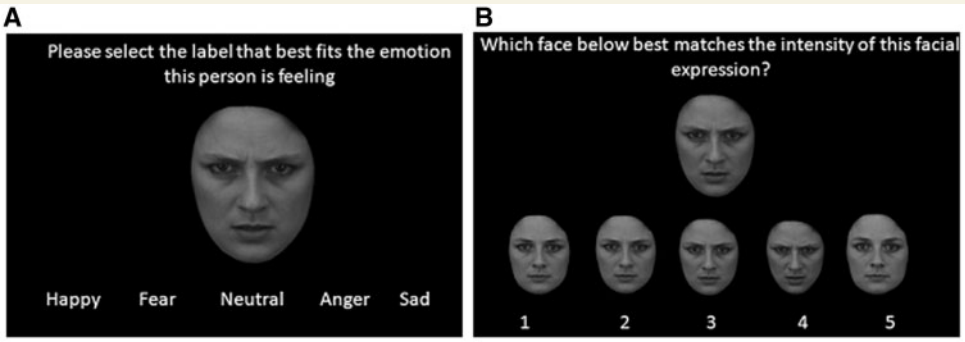

Figure 1 Example trials from the facial expression recognition task. (**A**) Participants select the emotion that best matches the expression displayed. (**B**) Participants select the face that best matches the intensity of the emotion displayed on the central face.

Results

Baseline demographics and screening material

Demographic information and screening neuropsychological testing are presented in Table 1.

Side-effects and adverse events

There were no significant adverse events attributable to the study medication. Following oxytocin administration, one subject reported soft stool, one experienced visual hallucinations and one participant with a history of prior episodes of palpitations and idiopathic hypokalaemia was found to have palpitations and hypokalaemia on the evening after oxytocin administration. Following placebo administration, three participants reported fatigue, three reported irritability and restlessness and one participant reported a hand tremor. The administration of oxytocin and placebo was not associated with any effects that broke the blind for study investigators, patients or family members. There were no drop-outs in the study. Two patients were unable to complete the auditory emotion recognition task due to task difficulty and elected to terminate the task; all patients completed all other study components.

Emotion recognition tasks

Facial recognition and intensity task

In the 2 (Treatment: oxytocin and placebo) × 4 (Emotion: fear, anger, happy and sad) × 4 (Expression intensity: 20, 40, 60 and 80%) ANOVA, no significant main effect of treatment was observed. However, a significant Treatment × Emotion interaction was observed [$F(3,57) = 3.917$), $P < 0.05$, partial $\eta^2 = 0.171$]. *Post hoc* *t*-tests showed reduced recognition of anger after oxytocin (mean correct = 49%) than after placebo (mean = 55%), [$t(19) = 2.10$, $P < 0.05$]. A trend of poorer recognition of fear following oxytocin versus placebo was also observed [$t(19) = 1.73$, $P < 0.05$ one-tailed] (Fig. 2).

A significant main effect of emotion [$F(3,19) = 3.2$, $P < 0.05$] showed that recognition of happy expressions was significantly better than any of the other emotions. There were no significant differences between sad, fear and anger recognition.

A significant main effect of intensity [$F(3,57) = 29.1$, $P < 0.05$] showed that emotion recognition was better for higher intensities compared with lower intensities. A significant emotion recognition by intensity interaction was also observed [$F(9,171) = 3.04$, $P < 0.05$, partial $\eta^2 = 0.138$]. *Post hoc* *t*-tests demonstrated that scores on happy recognition improved at lower levels of intensity and then levelled off, while recognition of negative emotions mostly improved at higher intensities: happy: 20–40% intensity [$t(19) = -4.11$, $P < 0.05$]; fear: 40–60% [$t(19) = -2.65$, $P < 0.05$] and 60–80% [$t(19) = -3.60$, $P < 0.05$]; sad 40–60% [$t(19) = -2.93$, $P < 0.05$] and 60–80% [$t(19) = -2.41$, $P < 0.05$]; anger 20–40% [$t(19) = -3.0$, $P < 0.05$] and 60–80% [$t(19) = -4.27$, $P < 0.05$].

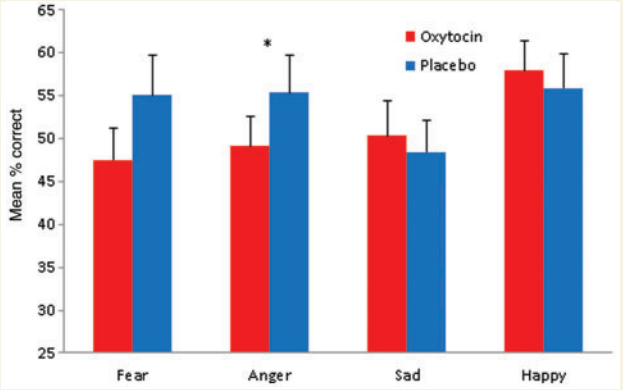

Figure 2 In the facial recognition task, a significant Emotion × Treatment interaction demonstrated a reduction in recognition of angry faces following oxytocin administration compared with placebo (*$P < 0.05$), and a trend of reduced fear recognition ($P < 0.05$ one-tailed) following oxytocin compared with placebo.

In the 2 (Treatment) × 4 (Emotion) ANOVA on intensity judgements, there were no significant main effects of treatment nor emotion.

Vocal affect recognition

No significant main effects of treatment or Treatment × Emotion interactions on vocal affect recognition were identified. A significant main effect of emotion was observed [$F(5,85) = 3.2$, $P < 0.05$]. *Post hoc* *t*-tests indicated that patients had the greatest difficulty recognizing fearful vocal affect and that patients were better at recognizing expressions of surprised and neutral compared with negative emotions (Supplementary Table 1): per cent correct responses to surprise (mean = 21.5), sad (mean = 19.4), happy (mean = 13.2), disgust (mean = 12.2), anger (mean = 6.3), fear (mean = 4.2); fear versus sad [$t(17) = -2.35$, $P < 0.05$]; fear versus happy [$t(17) = -2.19$, $P < 0.05$]; fear versus neutral [$t(17) = -4.27$, $P < 0.05$]; fear versus surprise [$t(17) = -3.40$, $P < 0.05$]; neutral versus disgust [$t(17) = 2.57$, $P < 0.05$]; neutral versus anger [$t(17) = 2.99$, $P < 0.05$]; surprise versus anger [$t(17) = 2.36$, $P < 0.05$]; and surprise versus disgust [$t(17) = 2.17$, $P < 0.05$]. There was no significant main effect of intensity or Intensity × Emotion interaction.

Mind in the eyes

A significant main effect of treatment was observed on correct responses [$F(1,19) = 4.5$, $P < 0.05$, partial $\eta^2 = 0.192$), in which performance following oxytocin treatment (mean = 54%) was worse than performance following placebo (mean = 59%) (Supplementary Table 1).

Behavioural scales

Neuropsychiatric Inventory

A significant difference in total scores (frequency × severity) on the Neuropsychiatric Inventory was observed during Day 1

following oxytocin administration versus placebo administration [$t(19) = -2.19$, $P < 0.05$]. The estimated score difference between oxytocin and placebo treatment on Day 1 was −2.70 points ± 1.24 (±SEM) (95% confidence interval: −5.29, −0.11) (Fig. 3). Compared with baseline, administration of oxytocin was associated with a mean 13% improvement in Neuropsychiatric Inventory scores compared with a mean 3% improvement for Day 1 placebo scores. *Post hoc* exploratory examination of sub-item scores on the Neuropsychiatric Inventory did not reveal any significant differences between individual sub-item scores for Day 1 of oxytocin versus placebo treatment (Table 2). Examination of sub-item scores suggests the significant differences in the oxytocin Day 1 and placebo Day 1 total Neuropsychiatric Inventory scores were driven by small reductions across multiple items including agitation/aggression, depression/dysphoria, apathy/indifference, disinhibition, irritability, aberrant motor behaviour, sleep and appetite and eating disorders.

Frontal Behavioural Inventory

A trend towards a difference in Frontal Behavioural Inventory raw scores for oxytocin versus placebo treatment on Day 1 was observed [$t(19) = -1.854$, $P < 0.08$] with $Mean_{oxytocin\ Day\ 1} = 12.9$ points (SD 4.3) and $Mean_{placebo\ Day\ 1} = 14.1$ points (SD 4.8) (Table 3). This reflected a 9% improvement in behaviour scores following oxytocin administration relative to baseline, compared with a 1% change in behaviour scores reported following placebo administration. There was no significant difference between oxytocin and placebo treatment scores on the Frontal Behavioural Inventory at 1 week following administration [$t(19) = -1.54$, not significant). *Post hoc* exploratory examination of sub-item scores did not reveal any significant differences between individual sub-item scores for oxytocin Day 1 versus placebo Day 1. As seen in Table 3, though not significant, examination of Frontal Behavioural Inventory subscores showed slightly lower raw scores for oxytocin Day 1 compared with placebo Day 1 on the

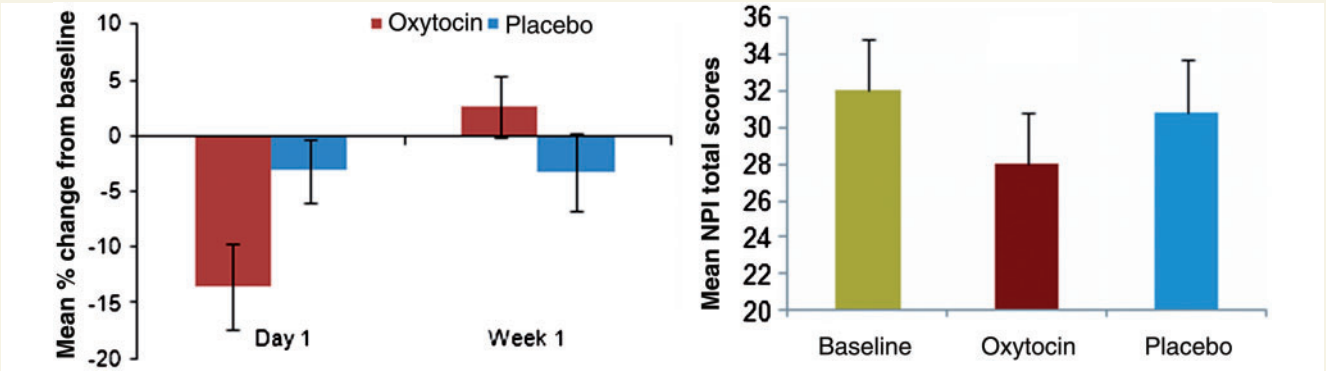

Figure 3 (**A**) Percentage change in total scores on the Neuropsychiatric Inventory as rated on Day 1 (8 h post drug administration) demonstrate improved FTD-related behaviours following 24 IU of intranasal oxytocin compared with placebo ($P < 0.05$). (**B**) Total raw scores on the Neuropsychiatric Inventory (NPI) demonstrate significant improvements on the evening following oxytocin administration compared with baseline and compared with placebo ($P < 0.05$).

Table 2 Mean ± SD Neuropsychiatric Inventory total and sub-item scores for baseline, Day 1 and Week 1 oxytocin and placebo treatments

NPI sub-items	Baseline	Oxytocin Day 1 post-treatment	Placebo Day 1 post-treatment	Oxytocin Week 1 post-treatment	Placebo Week 1 post-treatment
Total	32 ± 12.9	28.1 ± 12.2	30.8 ± 12.5	32.8 ± 13.4	31.0 ± 12.8
Delusions	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.7
Hallucinations	0.3 ± 0.9	0.3 ± 0.9	0.3 ± 0.9	0.6 ± 1.6	0.3 ± 0.9
Agitation/aggression	2.3 ± 2.5	2.3 ± 2.5	2.4 ± 2.7	2.8 ± 3.2	2.4 ± 2.8
Depression/dysphoria	2.0 ± 3.7	1.5 ± 3.3	2.0 ± 3.7	2.0 ± 3.5	2.0 ± 3.7
Anxiety	1.7 ± 3.4	1.1 ± 2.4	1.0 ± 2.1	1.5 ± 2.6	1.8 ± 3.3
Elation/euphoria	5.5 ± 3.8	1.3 ± 2.8	1.3 ± 2.8	1.5 ± 2.8	1.3 ± 2.8
Apathy/indifference	2.3 ± 3.4	6.4 ± 3.7	6.5 ± 3.5	7.1 ± 3.1	6.6 ± 3.6
Disinhibition	6.4 ± 3.8	3.7 ± 3.4	4.0 ± 3.3	3.9 ± 3.4	3.8 ± 3.3
Irritability	3.9 ± 3.1	1.7 ± 2.2	2.5 ± 3.0	2.5 ± 2.9	2.4 ± 2.8
Aberrant motor behaviour	2.4 ± 2.8	3.2 ± 4.4	3.4 ± 4.4	3.6 ± 4.5	3.4 ± 4.4
Sleep	2.8 ± 4.5	0.7 ± 2.0	1.3 ± 3.2	1.4 ± 3.2	1.0 ± 2.1
Appetite and eating disorders	2.5 ± 4.0	6.0 ± 3.4	6.3 ± 3.3	5.9 ± 3.1	6.2 ± 3.4

Table 3 Mean ± SD raw Frontal Behavioural Inventory total and sub-item scores

FBI sub-items	Baseline	Oxytocin Day 1 post-treatment	Placebo Day 1 post-treatment	Oxytocin Week 1 post-treatment	Placebo Week 1 post-treatment
Total	13.8 ± 4.6	12.9 ± 4.3	14.1 ± 4.8	14.2 ± 4.2	13.6 ± 4.6
Apathy	2.0 ± 1.0	1.9 ± 1.1	2 ± 1.0	1.8 ± 1.1	2.0 ± 1.1
Indifference/emotional flatness	2.2 ± 1.0	2.0 ± 1.1	2.3 ± 1.0	2.1 ± 1.0	2.2 ± 0.9
Perseverations and obsessions	2.2 ± 1.0	2.2 ± 1.0	2.2 ± 1.0	2.1 ± 1.0	2.4 ± 0.9
Inappropriateness	2.0 ± 0.9	1.9 ± 0.9	2.1 ± 0.9	2.1 ± 0.9	2.1 ± 0.8
Excessive jocularity	1.0 ± 1.3	0.9 ± 1.2	1.0 ± 1.3	1.0 ± 1.3	1.0 ± 1.3
Impulsivity/poor judgement	2.1 ± 1.1	2.1 ± 1.2	2.1 ± 1.1	2.3 ± 1.0	2.0 ± 1.2
Irritability	1.3 ± 1.2	1.2 ± 1.1	1.4 ± 1.3	1.3 ± 1.2	1.5 ± 1.2
Aggression	0.7 ± 1.1	0.5 ± 0.9	0.7 ± 1.1	0.6 ± 1.0	0.7 ± 1.1
Hypersexuality	0.5 ± 1.0	0.5 ± 1.0	0.5 ± 1.0	0.5 ± 1.0	0.5 ± 1.0

Scores for the nine pre-selected sub-items for oxytocin and placebo treatments at baseline, Day 1 (~8 h after treatment) and 1 week post treatment. Higher scores indicate worse behaviour, maximum possible score for each item = 3, total maximum possible score = 27.

apathy, indifference/emotional flatness, inappropriateness, excessive jocularity, irritability and aggression sub-items.

Discussion

In this double-blind, placebo-controlled, cross-over challenge study, we found that a single dose of 24 IU of intranasal oxytocin was associated with a significant improvement in FTD-related neuropsychiatric behaviours 8 h following drug administration compared with placebo and compared with baseline ratings. As expected, given the short half-life of oxytocin, no significant effects were observed 1 week following medication administration. During facial expression recognition, results suggested a reduced identification of anger and a trend of reduced fear recognition following oxytocin administration compared with placebo. Oxytocin did not have significant effects on vocal affect recognition, but was associated with poorer accuracy on the Mind in the Eyes task.

Significant improvements in FTD-related neuropsychiatric behaviours following oxytocin demonstrated small non-significant changes across many of the sub-items, some of which were associated with social behaviour such as disinhibition, though some, such as sleep, were not. Whether oxytocin specifically improves prosocial behaviours in patients with FTD, as described in animal and healthy human data demonstrating oxytocin increased pair bonding, social recognition and memory, trust and cooperation (Kendrick *et al*., 1987; Pedersen *et al*., 1992; Insel and Young, 2001; Kosfeld *et al*., 2005; Baumgartner *et al*., 2008), will require further studies powered to assess differences in behavioural sub-item scores. Though oxytocin has been associated with reductions in stress and anxiety (Uvnas-Moberg *et al*., 1994; Heinrichs *et al*., 2003; Parker *et al*., 2005), this does not explain the current results as anxiety ratings on the Neuropsychiatric Inventory were not lower in oxytocin compared with placebo Day 1 treatments. It has been recently suggested that oxytocin-induced enhancement in affiliative and prosocial behaviours may be specific to members of one's in-group, while oxytocin may enhance defensive behaviours towards those considered to be in the out-group (De Dreu *et al*., 2010). In healthy humans, oxytocin enhances in-group measures of trust, love and favouritism but increases negative opinions and fear of the out-group (De Dreu *et al*., 2010, 2011). In the present study, the behaviours rated by caregivers on the Frontal Behavioural Inventory sub-items, and many of those on the Neuropsychiatric inventory, reflected interactions between the patient and their caregiver (i.e. in-group member interactions), as opposed to interactions with staff or other non-kin. If significant, whether such improvements in behaviour would extend to interactions with out-group members will require further study.

The present findings of reduced identification of negative facial expressions (anger and fear) are in line with several studies reporting reduced recognition of these emotions in healthy adults receiving intranasal oxytocin (Di Simplicio *et al*., 2009; Evans *et al*., 2010). It has been hypothesized that the improved trust and increased cooperative behaviour induced by oxytocin in healthy adults may in part result from a reduced perception of the level of threat conveyed in facial expressions or negative scenes (Heinrichs *et al*., 2004; Norman *et al*., 2010). This is in line with models that suggest that a heightened sensitivity to threat cues, as it occurs in disorders with elevated levels of anxiety such as post-traumatic stress disorder or borderline personality disorder, can increase the risk for aggressive behaviours (Shin *et al*., 2005; Dyck *et al*., 2009; Blair, 2010). It is important to note, however, some models of aggression posit that diminished recognition of facial expressions, particularly distress cues, increases the risk of aggressive behaviours, particularly in individuals with low levels of anxiety (Blair, 2001, 2003; Marsh and Blair, 2008). Studies examining caregiver ratings indicate that patients with FTD frequently display elevated levels of anxiety, which is highly correlated with their agitated and irritable behaviours (Porter *et al*., 2003). However, in the current study, just 5/20 patients had caregiver ratings that indicated elevated levels of anxiety; when these five individuals were excluded from the analysis, the significant improvement in Neuropsychiatric Inventory scores following oxytocin administration persisted. Thus, the present results suggest that in FTD, despite the presence of emotion recognition deficits and absence of elevated anxiety, neuropsychiatric behaviours are improved by oxytocin. Functional MRI studies indicate

that the effects of oxytocin on facial expression processing in healthy adults may be mediated via oxytocin-induced reductions in amygdala activation during threatening and fearful stimuli (Kirsch *et al*., 2005; Domes *et al*., 2007*a*; Labuschagne *et al*., 2010); however, in females, oxytocin may increase amygdala activity to fearful faces (Domes *et al*., 2010). As the amygdala is commonly affected by pathological changes early in the course of FTD, further study of the effects of oxytocin on reactivity in this region in FTD will be needed to clarify the neural basis for the observed effects.

To our knowledge, this is the first study to report the potential therapeutic effects of oxytocin on FTD symptomatology and social cognition. The results highlight the potential for the neuropeptide as a symptomatic treatment for FTD. However, the results of the current study are not sufficient to warrant the use of oxytocin as a treatment for FTD at present. Longer duration controlled trials with larger numbers of patients and repeated dosing are required before conclusions about the safety and therapeutic efficacy of oxytocin in FTD can be drawn. Oxytocin would not be expected to alter the progressive pathology of FTD, but larger scale studies can determine whether it can produce temporary, partial improvement of some symptoms.

Future studies combining oxytocin administration with functional imaging techniques and additional targeted cognitive tasks may elucidate the mechanisms for the observed behavioural effects in these patients with FTD. Further exploration of gender and in-group/out-group effects of oxytocin will further refine our understanding of the role for oxytocin in treatment of inappropriate social behaviours in FTD and related disorders. Work is currently underway to explore the safety and effects of repeated administration of oxytocin to target the core deficits in empathy and social behaviour in FTD.

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Supplementary material

Supplementary material is available at *Brain* online.

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