

The Use of Oxytocin to Improve Feeding and Social Skills in Infants With Prader–Willi Syndrome

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abstract

BACKGROUND AND OBJECTIVES: Patients with Prader–Willi syndrome (PWS) display poor feeding and social skills as infants and fewer hypothalamic oxytocin (OXT)-producing neurons were documented in adults. Animal data demonstrated that early treatment with OXT restores sucking after birth. Our aim is to reproduce these data in infants with PWS.

METHODS: We conducted a phase 2 escalating dose study of a short course (7 days) of intranasal OXT administration. We enrolled 18 infants with PWS under 6 months old (6 infants in each step) who received 4 IU of OXT either every other day, daily, or twice daily. We investigated the tolerance and the effects on feeding and social skills and changes in circulating ghrelin and brain connectivity by functional MRI.

RESULTS: No adverse events were reported. No dose effect was observed. Sucking assessed by the Neonatal Oral-Motor Scale was abnormal in all infants at baseline and normalized in 88% after treatment. The scores of Neonatal Oral-Motor Scale and videofluoroscopy of swallowing significantly decreased from 16 to 9 ($P < .001$) and from 18 to 12.5 ($P < .001$), respectively. Significant improvements in Clinical Global Impression scale scores, social withdrawal behavior, and mother–infant interactions were observed. We documented a significant increase in acylated ghrelin and connectivity of the right superior orbitofrontal network that correlated with changes in sucking and behavior.

CONCLUSIONS: OXT is well tolerated in infants with PWS and improves feeding and social skills. These results open perspectives for early treatment in neurodevelopment diseases with feeding problems.



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WHAT'S KNOWN ON THIS SUBJECT: In a Prader–Willi syndrome mouse model early oxytocin administration can strongly modify the course of the disease with short- and long-term effects on feeding and social skills. There are no data of oxytocin effects in human infants.

WHAT THIS STUDY ADDS: We report that 7-day intranasal oxytocin administration in infants with Prader–Willi syndrome is well tolerated and improves sucking/swallowing, social skills, and mother–infant interactions. Changes in brain connectivity of superior orbitofrontal cortex correlate with clinical improvements.

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TABLE 1 Clinical Characteristics of the Population at Birth and at Trial Inclusion

	Whole Population (<i>n</i> = 18)	Step 1 4 IU OXT Every Other Day (<i>n</i> = 6)	Step 2 4 IU OXT Every Day (<i>n</i> = 6)	Step 3 4 IU OXT Twice Daily (<i>n</i> = 6)
Boy	10 (56%)	3	5	2
Girl	8 (44%)	3	1	4
Genetic diagnosis				
Deletion	6 (33%)	4	1	1
Uniparental disomy	10 (56%)	1	5	4
Imprinting defect	2 (11%)	1	0	1
At birth				
Term (wk)	39 (30;42)	39	40	37
Prematurity (<37 wk)	4 (22%)	1	0	3
Caesarean delivery	11 (61%)	4	4	3
Apgar 1 min	8.5 (3;10)	9	8	5.5
Apgar 5 min	9.5 (5;10)	9.5	10	8.5
Weight (SD) ^a	−1.2 (−2.5;0.2)	−1.1	−1.4	−1.0
Length (SD) ^a	−1.1 (−3.0;0.9)	−1.6	−1.0	−0.8
Head circumference (SD) ^a	−0.2 (−2.8;2.4)	0.1	−0.2	−0.5
Tube feeding, <i>n</i> (%)	16 (89%)	5	5	6
At inclusion				
Age (mo)	3.9 (0.8;5.7)	4.5	3.8	3.9
Weight (SD) ^a	−1.4 (−2.7;0.5)	−1.6	−1.4	−0.7
Length (SD) ^a	−0.0 (−2.3;0.1)	−0.3	−0.0	−0.1
HC (SD) ^a	0.3 (−1.4;2.4)	−0.1	0.0	0.7
BMI (SD) ^a	−1.3 (−2.7;0.6)	−1.7	−1.6	−0.8
Tube feeding ^b	5 (28%)	1	1	3

Results are presented as median (minimum;maximum) or *n* = (%) (Whole Population column) and as median or *n* ("Step 1, 2, or 3" columns). Age is expressed as corrected age in premature babies. HC, head circumference;

^a SD scores at birth were calculated according to Usher and McLean⁹. SD scores at inclusion were calculated according to World Health Organization standards depending on sex and corrected age.

^b Age of infants still on tube feeding at inclusion: 1 and 1.8 months (step 3), 3.5 months (step 2), 5.3 months (step 3) and 6 mo (step 1). For the 11 infants who stopped NGT before inclusion, median duration of NGT was 1.5 months, ranging from 0.9 to 5.1 months.

Oxytocin (OXT) is a neuropeptide that plays an important role in modulating social interactions and mother–infant bonding.^{1–3} Quantitative neuroanatomical studies of postmortem human hypothalamic tissue from patients with Prader–Willi syndrome (PWS) have demonstrated a reduced number and volume of OXT neurons in the paraventricular nucleus in comparison with controls.⁴ Similarly, an alteration in the OXT system was described in PWS mouse models.⁵ Interestingly, a single OXT injection before the first 5 hours of life rescued 100% of the newborn *Magel2* knock-out (KO) mice from early death by restoring normal sucking activity.⁵ The *Magel2* KO mouse is now considered a mouse model for PWS and autism spectrum disorder (ASD) because truncated mutations

in the *Magel2* gene have been reported in some patients with ASD.⁶ Restricted production of mature OXT despite normal prohormone production was detected specifically in the hypothalamus of the *Magel2* KO pups. Altogether, these data suggest that OXT is involved in the pathophysiology of PWS and ASD.

PWS is a rare genetic disease caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11–q13 due to a deletion of chromosome 15q11–q13, maternal uniparental disomy, or an imprinting defect.⁷ This complex neurodevelopmental disease comprises several nutritional phases.^{7,8} From birth to 9 months, infants with PWS display severe hypotonia, poor interactions, and anorexic behavior with poor suck

that may cause life-threatening complications like aspiration. Breast feeding is impossible in most cases and nasogastric tube feeding (NGT) is started at birth in >80% of the infants to ensure normal weight gain.

Genetic diagnosis, which is now made in the first months of life,⁷ offers a unique opportunity for early treatment with OXT. In this study, we report the results of a proof-of-concept phase 2 study of a short course of intranasal OXT (7 days) in 18 infants with PWS <6 months of age on safety, feeding, and social skills, ghrelin levels, and brain connectivity.

METHODS

Patients

Eighteen infants with a genetic diagnosis of PWS were recruited and hospitalized in our French reference center for PWS. A detailed description of the population is shown in Table 1.⁹

Study Protocol

This proof-of-concept, monocentric phase 2 escalating dose study was divided into 3 steps of 7 days of OXT treatment (Syntocinon), each step recruiting 6 consecutive infants <6 months old. The flowchart and a diagram summarizing the time course of the study are shown in Fig 1 A and B, respectively. The study protocol has been registered at www.clinicaltrials.gov (identifier NCT 02205034) and was approved by the Research Ethics Committee of the Hospital of Toulouse. The complete study protocol is available at www.chu-toulouse.fr/-documents-disponibles-#art7101. Written informed consent was provided by the parents.

Evaluation of Tolerance

Each infant was examined daily by the team pediatrician, and blood pressure and heart rate

were monitored 3 times per day and for 2 hours after each OXT administration. An electrocardiogram was performed before and 5 min after each OXT administration. Biological parameters, glucose, potassium, sodium, and osmolality were assessed every 2 days. Diuresis and urinary density were monitored daily. After discharge, tolerance was evaluated by the parents with a standardized daily case report form and the local pediatrician in concert with the study team until the end of the study at day 30.

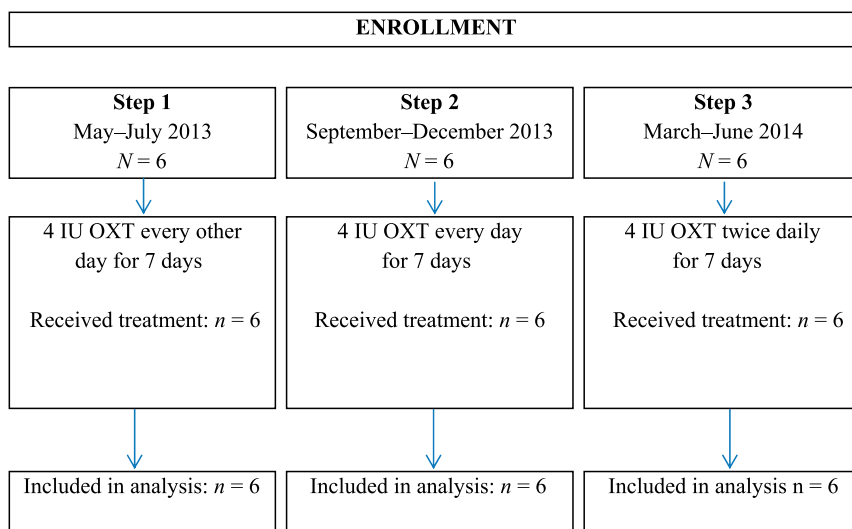
Evaluation of Oral Feeding Skills

Sucking and swallowing were evaluated before the first and after the last OXT administration. All evaluations were performed by the same speech-language pathologist (SLP) with expertise in PWS. We used the Neonatal Oral-Motor Assessment Scale (NOMAS) (Supplemental Table 4).¹⁰ Scores can vary between 8 and 28, with a score ≤ 10 defining a near-normal sucking pattern (Fig 2A). We also calculated the percentage of infants with a score ≤ 10 versus a score > 10 . A score ≤ 10 corresponds to a normal or near-normal sucking pattern without severe or life threatening respiratory complications.

The same day, a dynamic videofluoroscopy of swallowing was performed by the same SLP and scored with a grid of 9 relevant items used in routine practice (Supplemental Table 5). Videofluoroscopy was normal if the score was 11, and the maximum abnormal score was 29.

Finally, evaluations of behavior before and during feeding by using a Clinical Global Impression (CGI) scale (see Supplemental Table 6) were performed by the same team SLP concomitantly with the clinical scoring of sucking/swallowing.

A



B

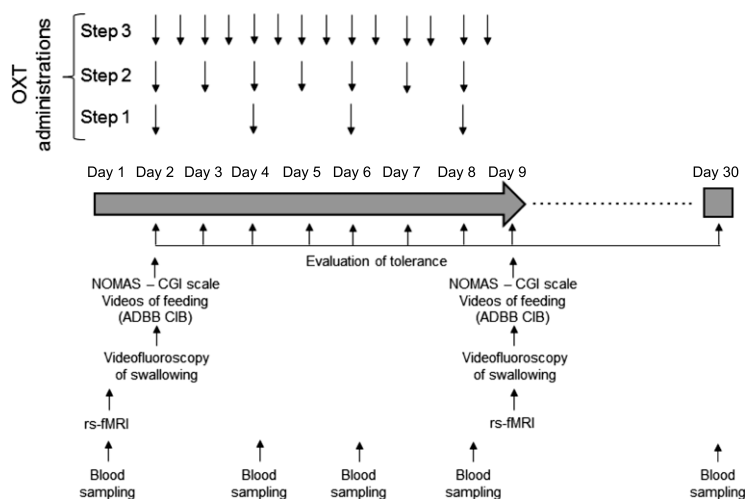


FIGURE 1

A, Flowchart of Study. B, Diagram summarizing the time course of the study.

Blind Evaluation of Social Skills

In addition, we assessed social withdrawal behavior and mother–infant interactions using the Alarm Distress Baby (ADBB) Scale and the validated Coding Interactive Behavior (CIB) Scale, respectively.^{11–13} The ADBB and CIB Scales were scored in a blinded manner on videos of feeding taken before and after OXT administration by 2 experts who did not participate in either designing the protocol or conducting the trial.

The ADBB Scale is a composite scale comprising 8 items with a score < 5 indicating normal behavior.¹¹ For the CIB Scale, each of the 42 items was rated from 1 (a little) to 5 (a lot) and grouped into 5 composites. In addition, according to the infant's age, 26 specific infant items based on Brazelton's Neonatal Behavioral Assessment Scale¹³ were rated and grouped into 2 additional composites (see Methods section in the Supplemental Information). Psychoanalytic infant observation

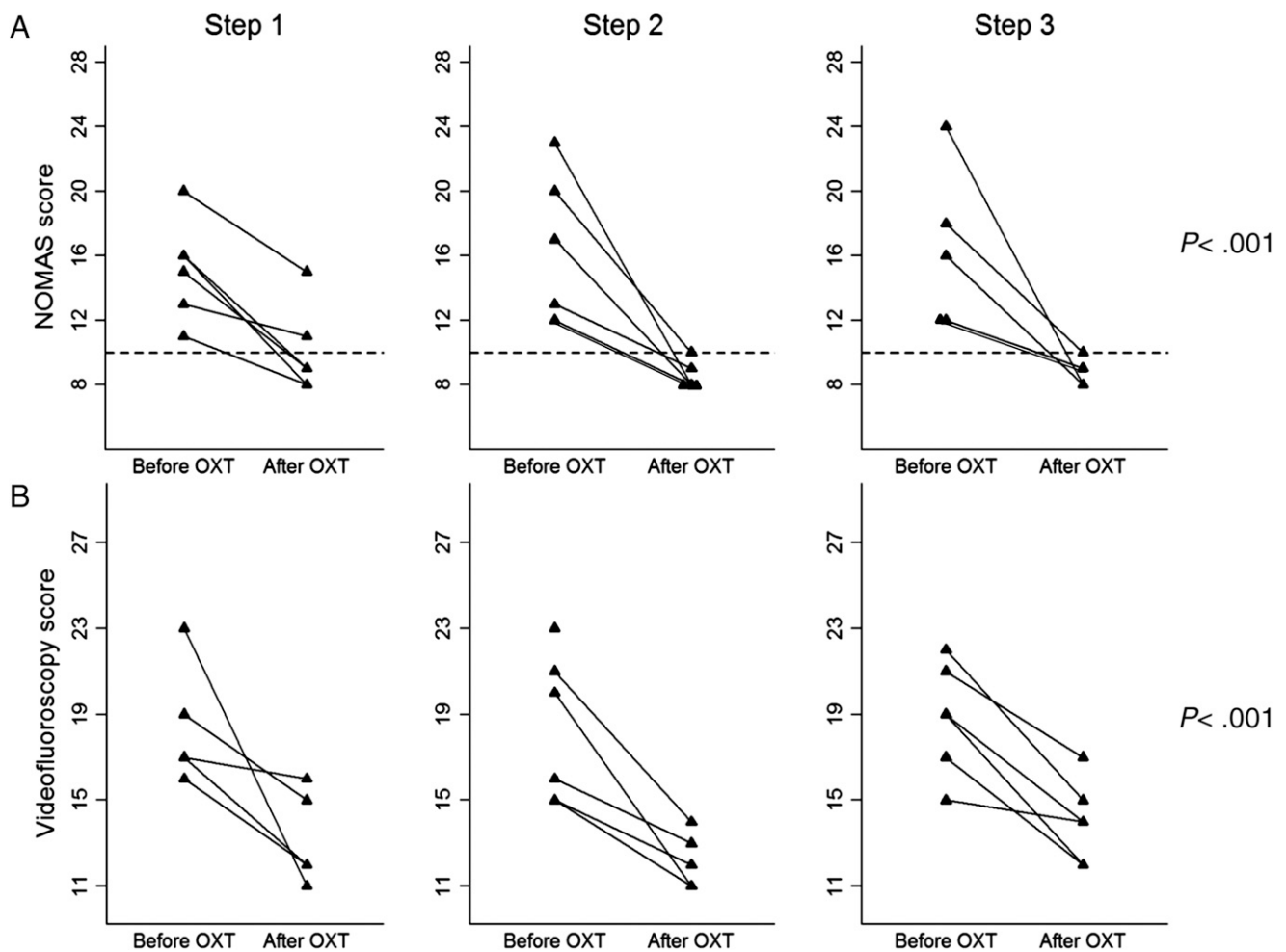


FIGURE 2

Evaluation of sucking/swallowing. A, NOMAS scores before ($N = 18$) and after the last OXT administration ($N = 17$). Score ≤ 10 defining a near-normal sucking pattern is represented as a dotted line. B, Scores of videofluoroscopy of swallowing before ($N = 18$) and after the last OXT administration ($N = 16$); P values refer to the whole group.

was performed with the parents' consent by a psychologist trained in E Bick's method before the first and after the last OXT administration at the hospital.¹⁴ During these observations, the psychologist provided parental support and highlighted the infant's skills with the parents.

Sampling and Hormone Assays

Blood sampling was performed every 2 days after a minimum of 3 hours of fasting. The samples were drawn into EDTA tubes with antiprotease 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (Sigma-Aldrich, St Louis, MO) at a concentration of 2 mg/mL for the

ghrelin and OXT measurements. Samples were stored at -20°C before the measurements were performed and were assayed not longer than 6 months after collection. Measurements of acylated (AG) and unacylated ghrelin (UAG) and OXT in blood were performed as described.¹⁵

Brain Connectivity Analysis During Resting State Using Functional MRI

The brain connectivity is defined as the temporal correlation of neuronal activity as evidenced by blood oxygen level-dependant (BOLD) signal of anatomically separated brain regions. With resting-state functional MRI (rs-fMRI), it is possible to investigate

the whole brain.¹⁶ Regions are said to be functionally connected if they demonstrate synchronous BOLD fluctuations at rest and then form a network. There are multiple resting-state networks that pertain to different brain functions that can be detected from the time-series scans. Independent Component Analysis (ICA)-based methods¹⁷ are the most commonly used and display high level of consistency.¹⁸ To investigate the effect of OXT on brain connectivity, we scanned 17 of 18 infants at rest without sedation before and on the seventh day after the first OXT administration. We applied ICA (Group ICA fMRI Toolbox [GIFT], <http://mialab.mrn.org/>)

software/gift/, Version 4.0a)¹⁸ to find a set of statistically independent spatial components. This group analysis allowed us to identify important networks and then provide the associated map for each subject and each condition where the value in each voxel is a z score measure of the pixel connectivity to the network (see Methods in Supplemental Information).

Long-term Observational Data

Although clinical follow-up was not part of the phase 2 trial, we routinely followed 16 of the 18 children for 2 to 3 years and compared them with 16 age-matched untreated children with PWS also followed in our reference center.

Statistical Analysis

Data are presented for the whole population and for each dose step. The continuous variables were expressed as medians and ranges and the categorical data as numbers and percentages. Continuous variables before and after treatment were compared by using Wilcoxon signed rank tests in the whole population and in each dose step. The score changes were compared between dose steps by using Kruskal–Wallis ranking tests when significant evolution was observed in the whole study group. Changes in the connectivity z score before and after OXT treatment were measured with a paired *t* test. Correlations between connectivity z score changes in rs-fMRI and changes in the oral feeding scales (NOMAS, videofluoroscopy) and behavior changes (CGI, ADBB, CIB) were estimated for the whole sample by the Kendall τ -b coefficient. Comparative analyses of long-term data between early OXT-treated infants and age-matched untreated infants were conducted by using Mann–Whitney or χ^2 tests. Data analysis was performed with Stata version 11.2 software (Stata Corp,

College Station, TX). *P* values $\leq .05$ were considered statistically significant.

RESULTS

Tolerance

We observed no adverse event in relation to OXT for any of the parameters specifically surveyed and no other event occurred during the 7 days of OXT administration and up to day 30. Overall, the tolerance to OXT was excellent, with no cardiovascular or antidiuretic arginine vasopressin-like effects. Plasma OXT levels were highly variable before and after OXT administration and did not significantly change in each step (data not shown).

Effect of OXT on Oral Skills

The NOMAS score significantly improved after treatment for the whole group, with a change in the median score from 16 to 9 ($P < .001$). At baseline, the score varied widely from 11 to 24 with no infant having a normal score. After OXT treatment, 8 infants (47%) reached a score of 8, which is strictly normal and 15 (88%) had a score ≤ 10 , meaning that they displayed a near-normal sucking pattern (Fig 2A). Only 2 patients included in step 1 did not normalize their score after treatment. Overall, the changes in NOMAS scores did not differ between the 3 dose steps ($P = .504$).

The scores of videofluoroscopy of swallowing significantly improved after treatment for the whole group from a median value of 18 to 12.5 ($P < .001$) and in each dose step (see Fig 2B). At baseline, 13 infants out of 16 displayed pharyngeal stasis that can drive inhalation, whereas only 2 infants displayed it after OXT treatment. Improvement was obvious as is shown in the videofluoroscopy of swallowing before and after OXT of 1 infant (see Supplemental Video 1 and 2). No significant difference

according to dose step ($P = .588$) was found.

Effect on Behavior and Social Skills

As shown in Fig 3A, the CGI score significantly improved after treatment from a median score of 3 to 6 before feeding ($P = .001$) and from 0 to 3.5 during feeding ($P = .001$) in the whole group.

At baseline, the median ADBB score was 6.5, with 62% of the infants with an ADBB score ≥ 5 (value of normal score, < 5). The median score significantly improved for the whole group from 6.5 to 3.5 ($P = .005$), with a normal score in 81% of infants after OXT treatment (Fig 3B). We observed significant improvements on 4 of the 8 items: facial expression, from a median score of 1.0 to 0.0 ($P = .005$); eye contact, from 1.0 to 0.5 ($P = .043$); general level of activity, from 1.0 to 0.0 ($P = .028$); and relationships, from 1.0 to 0.0 ($P = .006$) (Fig 3C). For the total ADBB score as well as for these 4 items, the observed changes did not significantly differ between the 3 steps. Figure 3D shows the changes in composites of the CIB scale for the whole group. We observed significant improvements after treatment on 4 out of 7 composites: parental sensitivity, from a median score of 2.47 to 3.08 ($P = .033$); dyadic reciprocity, 2.43 to 2.75 ($P = .009$); child social engagement, 1.91 to 2.50 ($P = .001$); and child state, 2.40 to 3.20 ($P = .002$). These significant changes did not differ between the 3 steps.

Infants' observations revealed an improvement in the parents' interrelations with the baby in gaze, holding, and handling.

Effect of OXT on Circulating Ghrelin

In PWS infants, AG levels significantly increased between baseline and, respectively, 2 days (from 189 to 307 pg/mL, $P = .037$) and 4 days (from 189 to 370 pg/mL, $P = .044$) after the first OXT administration (Fig 4A). No significant changes were observed

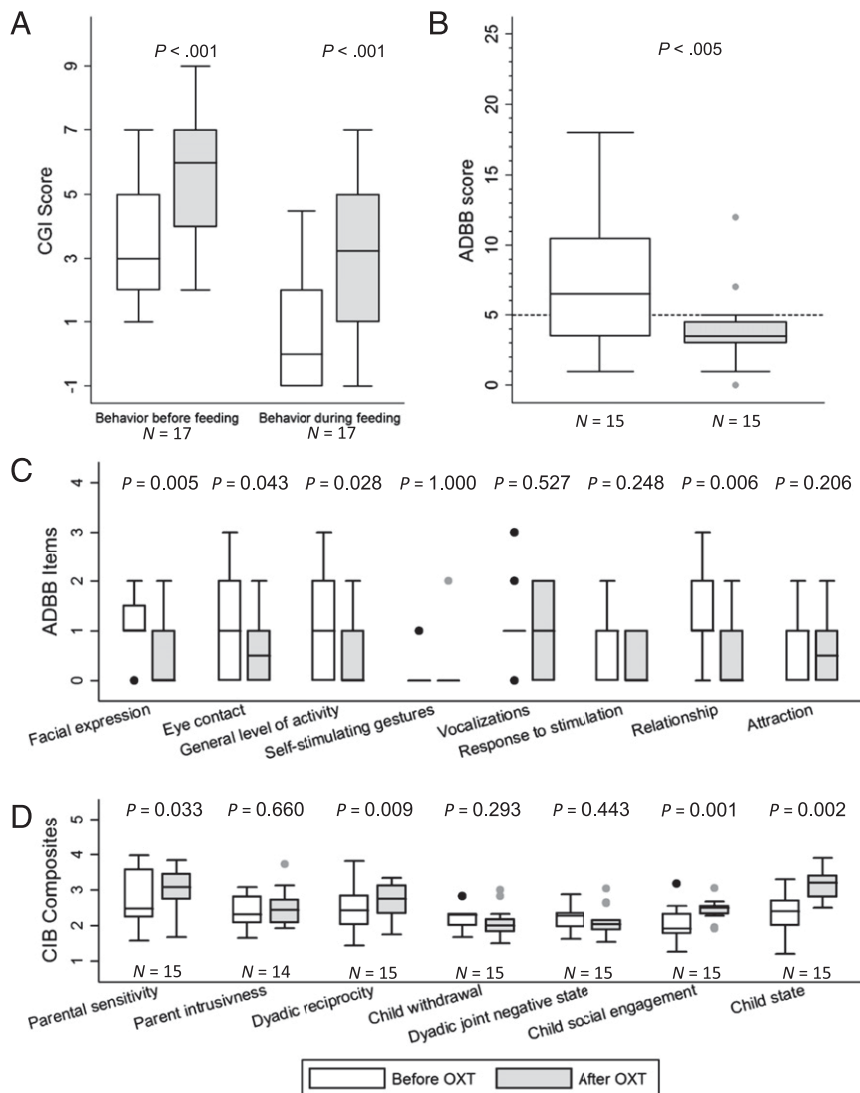


FIGURE 3
Evaluation of behavior and social skills before (white box) and after (gray box) OXT treatment. A, CGI scale scores. B, Total ADBB scale scores. C, Composites ADBB scale scores. The dotted line represents the cut-off value of a normal score. D, Composites of the CIB scale scores.

in UAG levels (Fig 4B). Changes between baseline and 4 days after the first OXT administration did not significantly differ between the 3 dose steps ($P = .889$).

Effects of OXT on Brain Connectivity Analysis Using rs-fMRI

Among the 17 infants who were evaluated twice, 7 infants were discarded either because the head motion exceeded our limits or because the images showed a significant static magnetic field (B0) inhomogeneity. Ten infants (4 in

step 1, 3 in step 2, and 3 in step 3) were kept for additional analysis. Figure 5A shows the regions with high connectivity (z score > 3.1) (red regions) obtained after ICA forming the network comprising 15 cerebral areas we selected for additional analysis (see Methods in the Supplemental Information). As shown in Fig 5B, inside this network, only the connectivity of the right superior orbitofrontal cortex (OFC) increased after OXT treatment (paired t test, $P < .05$; family-wise error corrected). In addition, the

mean change calculated over all the voxels in this area for each subject was correlated with the changes in NOMAS (τ -b = -0.396), the CIB child social engagement composite (τ -b = 0.555), and the CIB child state composite (τ -b = 0.535) (Fig 5C).

Long-term Observational Data Collected During Routine Follow-up

As shown in Table 2, we observed no significant differences in height, weight, BMI, or body composition at a median age of 26.5 months (range, 13 to 35 months), thus documenting the excellent long-term tolerance of early OXT treatment. Although we did not observe a difference in the age at walking between the 2 groups, 81% of the OXT-treated infants were able to crawl versus 13% of the untreated infants. Indeed, toddlers with PWS generally start walking without ever having learned to crawl. The ability to crawl observed after OXT treatment is in line with our observations of better muscle tone and motor coordination skills in these toddlers. Moreover, we observed that the OXT-treated infants displayed higher social skills and were more engaged in relationships than the children of comparable age who did not receive early OXT treatment.

DISCUSSION

This proof-of-concept study demonstrates that a short course of repeated intranasal OXT administration is well tolerated and improves oral feeding and social skills in infants with PWS. Given the preclinical data for OXT, the early diagnosis of PWS and the possible role of OXT in the pathophysiology of the disease, PWS is a good model to study the effects of early OXT administration. The effects on oral feeding and social skills in human infants are reported in this study for the first time. In our study, an abnormal sucking pattern was present at baseline for all infants and was normalized in 88% of them after

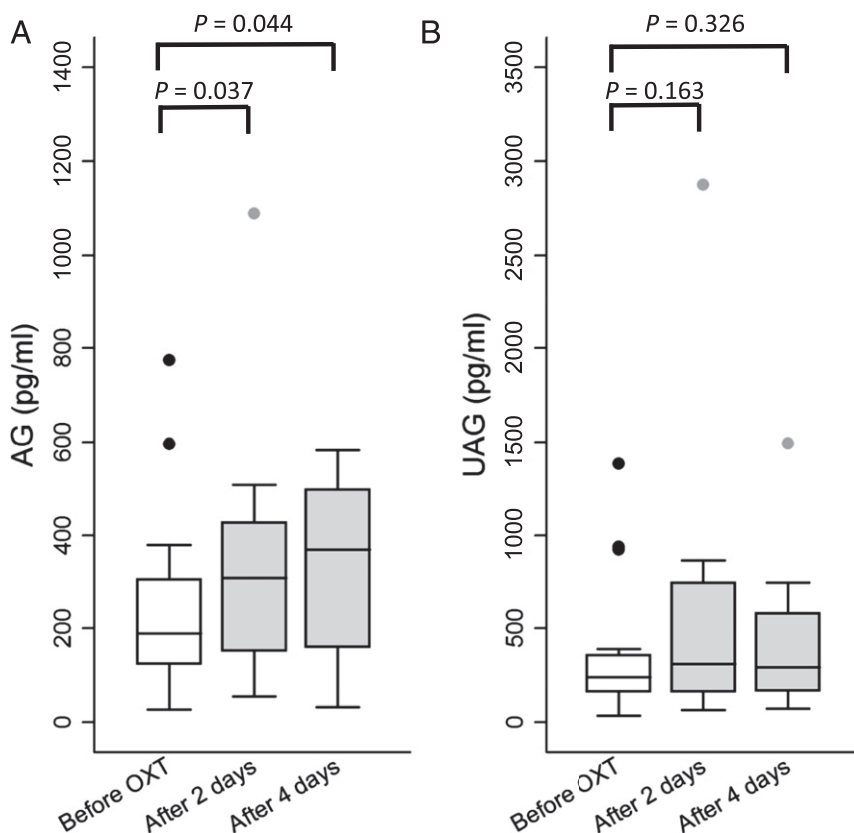


FIGURE 4

A, Evolution of circulating fasting AG; and B, Evolution of circulating fasting UAG before the first OXT administration (white boxes) and 2 days and 4 days after the first OXT administration (gray boxes) in 16 infants. Only AG levels significantly increased with OXT treatment.

OXT treatment. Such improvement is highly clinically relevant because there was a complete rescue from the life-threatening respiratory complications of poor feeding skills in this population. It is likely that OXT improves oral motor function of the face and head, including the larynx and pharynx. Interestingly, these structures and the nerves that innervate them were described as part of a system (polyvagal theory)¹⁹ that permits social engagement and communication.¹ In addition, we observed a significant increase in circulating AG, which is called “the hunger hormone,” after OXT treatment that may counterbalance the excess of UAG, which possibly drives anorexia, as discussed in our recent publication.²⁰ Interestingly, increased gastric ghrelin gene expression after OXT treatment has been recently reported in neonatal

pigs.²¹ The stimulating effect of OXT on ghrelin secretion occurs via the OXT receptor in a cellular model.²² Importantly, we document the positive effects of OXT treatment on behavior and social engagement and on mother–infant interactions. After OXT treatment, the infants were more alert, less fatigable, more expressive, and had less social withdrawal. They initiated mutual activities and were more engaged in relationships through gaze, behavior, and vocalizations. These modifications helped the parents to be more sensitive. The mother–infant dyad was less restricted and there was a better reciprocal exchange, thus engaging the dyad in a positive transactional spiral as well as optimizing feeding. This improvement was also supported by infant observation in gaze, holding, and handling. In humans, “mutual

gaze” is the most fundamental manifestation of social attachment.¹ Indeed, we are aware that these changes may have been due to OXT and/or to the support and guidance provided by the expert team to the parents.

Importantly, these early effects of OXT persisted 3 weeks after the last OXT administration.

The follow-up until 2 to 3 years of age documents the excellent tolerance and possible long-lasting effects of early OXT treatment on social skills, relationships, and psychomotor development, which is in line with the preclinical data in *Magel2* KO mice.²³

We also document the increased connectivity of the right superior orbitofrontal network after infants’ treatment with OXT. The OFC contains major cortical representations of taste and food texture and olfactory and somatosensory inputs from both the mouth and other parts of the body, as well as information about real faces, gestures, and movement.²⁴ Overall, the OFC is involved in motivational behavior, such as feeding and drinking, emotional decision-making, and social behavior by implementing learning mechanisms through decoding the reward and punishment values of stimuli.²⁵ We found it highly relevant that changes in right superior OFC connectivity were correlated with changes in infant oral motor skills and CIB composite scores. Of note, a link between oral feeding in premature babies and cognitive development at 2 years was recently documented.²⁶ Taken together, these findings suggest the hypothesis that the observed increased right superior OFC connectivity after OXT treatment preserves OFC function, which may be important for long-term effects.

The preclinical data supporting the protective action of maternal OXT during delivery by preventing

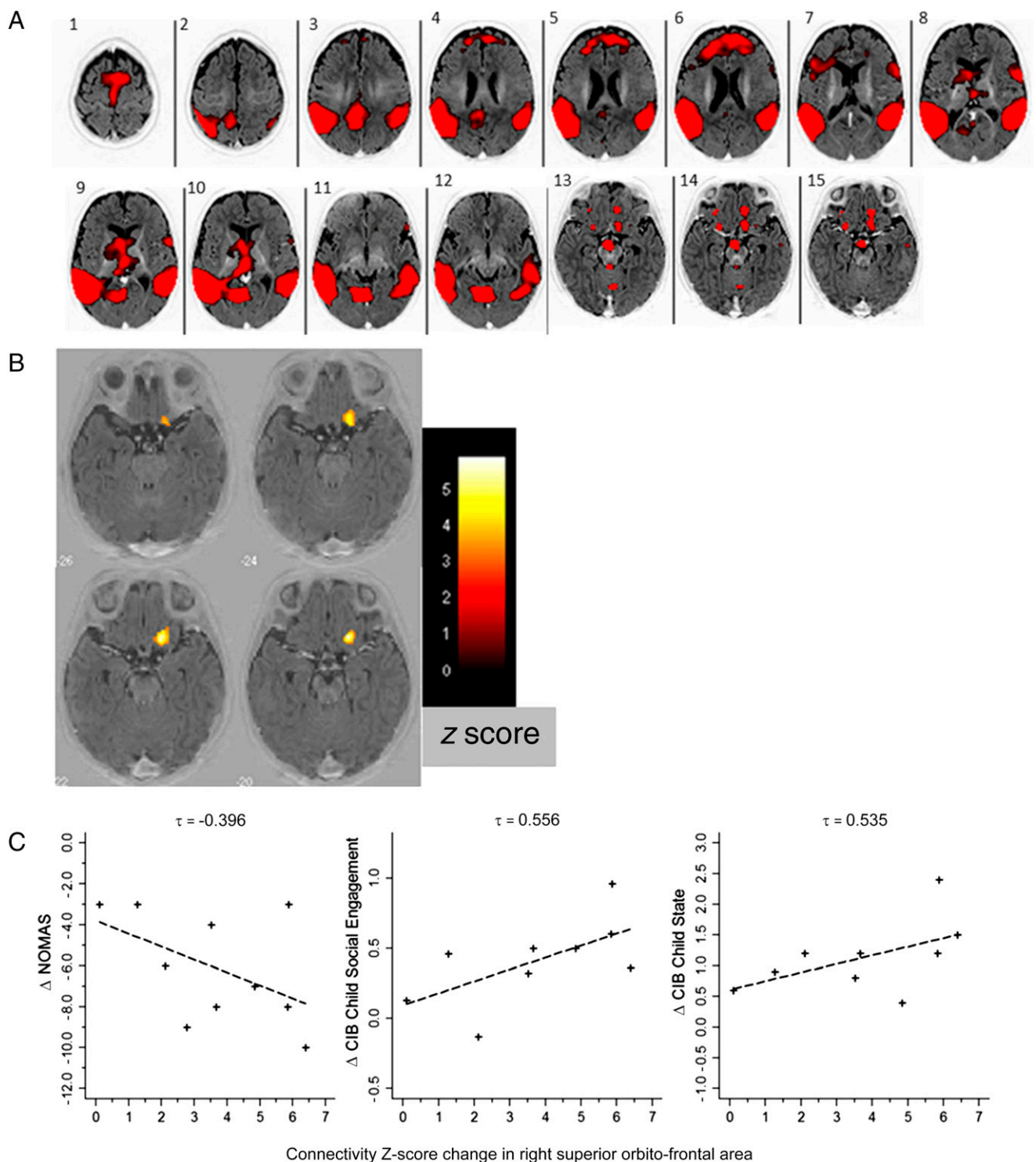


FIGURE 5

Brain connectivity studies. A, High connectivity (z score >3.1) regions in red forming the network selected for additional analysis. B, Increased connectivity z score after OXT in the right superior orbitofrontal area (yellow). C, Correlations between connectivity z score changes in right superior orbitofrontal area and changes in NOMAS score and CIB subscores.

the deleterious effects of enhanced activity of GABA signaling,²⁷ in addition to the current evidence of changes in brain connectivity after OXT administration in infants <6

months old, suggest a continuum in the role of OXT from birth to early postnatal life.

In our study, we were not able to document any difference between the

3 doses of OXT used, which suggests that a little amount of OXT is required to get the effects. The fact that low dose is as efficient as higher doses may be due to the stimulation of the

TABLE 2 Long-term Observational Data of OXT-Treated Infants During Follow-up and Comparison With Age-Matched Untreated PWS Infants

	OXT-Treated PWS (<i>n</i> = 16)	Untreated PWS (<i>n</i> = 16)
Age, m (SD)	26.5 (13;35)	26 (10;35)
Sex ratio (% boys)	62.5%	37.5%
Height (SD) ^a	−0.2 (−2.3;1.3)	−0.5 (−3.5;1.8)
Weight (SD) ^a	−0.8 (−3.3;2.2)	−0.835 (−3.0;6.0)
BMI (z score) ^b	−0.9 (−3.2;1.6)	−0.6 (−2.8;4.1)
Fat mass	18% (<i>n</i> = 10)	20% (<i>n</i> = 15)
Lean mass	77.8% (<i>n</i> = 10)	79.7% (<i>n</i> = 15)
Age at start of growth hormone treatment, median (minimum, maximum)	10 (8;13)	11 (6;25)
Walking age, median (minimum, maximum)	24(18;30); <i>n</i> = 10	24.5(13;38); <i>n</i> = 10
Crawling*	81%	13%

Results are presented as median (minimum;maximum) or %. Fat mass and lean mass were measured by dual energy radiographic absorptiometry.

^a SD scores were calculated according to World Health Organization standards depending on sex and corrected age.

^b BMI was expressed as z score, adjusted for age and sex.

* *P* = .04 (χ^2 test).

endogenous somatodendritic release of OXT regulated by exogenous OXT via the OXT receptor in a positive feedback loop reported in electrophysiological studies.²⁸

CONCLUSIONS

These results reveal that a short course of intranasal OXT administration rescues oral feeding and social skills in infants with PWS. These promising effects need to be confirmed by a phase 3 trial. In addition, it will be important to thoroughly evaluate the long-term effects to determine if and how OXT changes the course of PWS. We anticipate that these results will also have a broad impact on infants with severely impaired sucking and

infants with an early diagnosis of ASD.

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ABBREVIATIONS

ADBB: Alarm Distress Baby
AG: acylated ghrelin
ASD: autism spectrum disorder
BOLD: blood oxygen level-dependant
CIB: coding interactive behavior
CGI: clinical global impression
GIFT: Group ICA fMRI Toolbox
ICA: Independent Component Analysis
KO: knock-out
NGT: nasogastric tube feeding
NOMAS: Neonatal Oral-Motor Assessment Scale
OFC: orbitofrontal cortex
OXT: oxytocin
PWS: Prader–Willi syndrome
rs-fMRI: resting-state functional MRI
SLP: speech–language pathologist
UAG: unacylated ghrelin

Dr Tauber participated in conception and design of the study, conducted the study, and participated in data analysis and interpretation and manuscript writing and review; Dr Boulanouar performed functional MRI analysis and participated in the manuscript writing; Drs Diene and Cabal-Berthoumieu participated in conception and design of the study, conducted the study, and participated in data collection and manuscript review; Mrs Ehlinger performed all statistical analyses and participated in the manuscript writing; Dr Fichaux-Bourin performed all the sucking/swallowing as well as Clinical Global Impression evaluations; Mrs Molinas and Mrs Valette conducted the study and participated in data collection and analysis and in manuscript writing; Mrs Faye conducted the study and participated in data collection and analysis; Mrs Pourrinet performed infant observations and participated in the manuscript writing; Dr Cessans participated in data collection; Drs Viaux-Sauvelon and Guedeney performed Coding Interactive Behavior Scale assessments and analysis and participated in the manuscript writing; Dr Bascoul performed Alarm Distress Baby Scale assessments; Dr Delhanty performed ghrelin measurements and participated in the manuscript writing; Drs Geenen and Martens performed oxytocin measurements and participated in the manuscript review; Dr Muscatelli participated in conception of the study based on preclinical data and manuscript review; Drs Cohen and Consoli participated in manuscript writing and review; Dr Payoux participated in conception of the study and analysis of functional MRI data; Dr Arnaud participated in the conception and design of the study, supervised data analysis, and participated in manuscript writing; and Dr Salles participated in the conception and design of the study and critical revision of the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT 02205034).

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The Use of Oxytocin to Improve Feeding and Social Skills in Infants With Prader–Willi Syndrome

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