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A B S T R A C T

Background: Infant-mother interaction is a set of bidirectional processes, where the baby is not only affected by the influences of his caregiver, but is also at the origin of considerable modifications. The recent discovery of biological correlates of synchrony during interaction validated its crucial value during child development. Here, we focus on the paradigmatic case of Prader-Willi Syndrome (PWS) where early endocrinal dysfunction is associated with severe hypotonia and early feeding disorder. As a consequence, parent-infant interaction is impaired. In a recent study (Tauber et al., 2017), OXT intranasal infusion was able to partially reverse the feeding phenotype, infant's behavior and brain connectivity. This article details the interaction profile found during feeding in these dyads and their improvement after OXT treatment.

Methods: Eighteen infants (≤6 months) with PWS were recruited and hospitalized 9 days in a French reference center for PWS where they were treated with a short course of intranasal OXT. Social withdrawal behavior and mother-infant interaction were assessed on videos of feeding before and after treatment using the Alarm Distress Baby (ADBB) Scale and the Coding Interactive Behavior (CIB) Scale. Raters were blind to treatment status.

Results: At baseline, infants with PWS showed hypotonia, low expressiveness of affects, fatigability and poor involvement in the relationship with severe withdrawal. Parents tended to adapt to their child difficulties, but the interaction was perturbed, tense, restricted and frequently intrusive with a forcing component during the feeding situation. After OXT treatment, 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. They had a better global tonicity with better handling. These modifications helped the parents to be more sensitive and the synchrony of the dyad was in a positive transactional spiral.

Conclusion: Dys-synchrony can be induced by children's pathology as well as parental pathology with emotional and developmental impact in the both cases. The PWS paradigm shows us the necessity to sustain early parents-child relationship to avoid establishment of a negative transactional pattern of interaction that can impact child's development.

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1. Introduction

1.1. Synchrony and the role of OXT during early interaction

The impact of the quality of parent-child relationships on children's social, emotional and cognitive development has been highlighted for years by many studies (Feldman, 2007; Harrist & Waugh, 2002). These studies have shown significant correlations between the quality of the parent-child relationship and children's developmental outcomes (e.g., social competence) (Saint-Georges et al., 2013), emotion regulation (Field, 1987), and access to symbolic play (Keren, et al., 2005). As a consequence, dysregulation in parent-child interactions has been linked to the development of children's problematic behaviors (Choe et al., 2013; Field, 1987). Additionally, atypical parent-child interactions are suspected of contributing to pervasive developmental impairments among infants, such as autism (Wan et al., 2013).

Currently, the relationship between the baby and his environment is considered as a set of bidirectional processes, where the baby is not only affected by the influences of his environment, but also is still at the origin of considerable modifications: one of which reveals the concept of interaction (Feldman, 2007). The interaction defines itself as the mutual influence, two subjects with reciprocity and interdependence. Generally, the interaction is defined as all the dynamic phenomena, which take place in the time between an infant and his different partners (Delaherche et al., 2012).

In analyzing synchrony as the unfolding dance between matched and mismatched states, Tronick (Tronick & Cohn, 1989) pointed out that mother and child spend most of their playtime in mismatched, rather than matched states, yet most of the mismatch is repaired in the next step. By highlighting the concepts of mismatch and repair, the theoretical focus shifts to the way dyads repair moments of miscoordination as the central component of intimate relationships and of the synchrony experience. A major function of the co-regulatory process, therefore, is the self-correcting capacities of the dyad and the infant's growing appreciation that relationships are not always fully attuned to one's needs. (Leclere et al., 2014)

Given that the relationship between an infant and his caregiver is bidirectional in nature, the dyad should be thought of as a dynamically interacting system. An infant can influence the care he receives from the caregiver by the ways he behaves. Given the dynamic relationship between an infant and his caregiver, a specific interest in the flow characterizing the exchange of information during infant-caregiver interactions has emerged, leading to the study of rhythm (meaning balance between partners), reciprocity (meaning partners' ability to show adaptation to each other), and synchrony (meaning the dynamic and reciprocal adaptation of the temporal structure of behaviors between interactive partners). The recent discovery of both biological correlates of behaviorally synchronic phenomena and statistical learning validated the crucial value of studying synchrony during child development (Feldman, 2007; Gordon et al. 2017; Leclere et al., 2014). This synchrony phenomena remains true accross modalities and behaviors whether focusing on speech turns (e.g. Weisman et al., 2015; Jaffe et al., 2001), motion (Leclère et al., 2016), head movements (e.g. Hammal et al., 2015) and smile (Messinger et al., 2008).

Oxytocin (OXT) is a neuropeptide that plays an important role in modulating social interactions and mother–infant bonding. (Carter, 2014; Numan and Young, 2016; Insel 2010). Specifically, OXT has been shown to shape early interaction by increasing reciprocity first in animal models (Insel, 2010) and more recently in humans as well (Weisman et al., 2012; 2013).

When one of the partners is not healthy, whether it is the mother (e.g. depression; neglectness) or the infant (e.g. autism), the interactive process is affected (Leclere et al., 2014).

We proposed in this article to focus on the paradigmatic cases of Prader Willi Syndrom (PWS) where early endocrinal dysfunction is linked with low level of Oxytocine (OXT), severe hypotonia and early feeding disorder and by this way perturbs parents-child early interactions.

1.2. Prader Willi Syndrome (PWS) as a paradigm to study OXT early deficit and early Dyssynchrony

PWS is a rare genetic disease caused by the lack of expressionof paternally inherited imprinted genes on chromosome 15q11-q13. This complex neurodevelopmental disease comprises several nutritional phases and is associated to behavioral disorder in teenage. 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. Breastfeeding is impossible in most cases and nasogastric tube feeding (NGT) is started at birth in >80% of the infants to ensure normal weight gain. Behavioral problems are frequent and usually emerge around four years of age, and the characteristic profile is that of obsession with food, temper tantrums, aggression, stubbornness, skin-picking, and controlling and manipulative behavior (Dykens, Leckman, & Cassidy, 1996; Clarke et al., 2002). Intellectual deficiency is variable and associated with learning disability and verbal expression disability added to psychological and behavioral disorder.

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 (Swaab et al., 1995). Similarly, an alteration in the OXT system has been described in PWS mouse models (Schaller et al., 2010). Interestingly, a single OXT injection before the first 5 h of life rescued 100% of the newborn Magel2 knock-out (KO) mice from early death by restoring normal sucking activity (Schaller et al., 2010). 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 (Schaaf et al., 2013). 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.

In a recent proof of concept trial, our team (Tauber et al., 2017), showed that OXT intranasal infusion was able to partially reverse feeding phenotype and infant's behavior. It was also showed that changes in brain connectivity, assessed by functional MRI, correlate with changes in sucking and behavior. Here we aimed to detail early interaction improvement after OXT intranasal infusion based on the study of infant social engagement and parent-infant synchrony.

2. Methods

2.1. Patients

Eighteen infants less than 6 months old with a genetic diagnosis of PWS were recruited and hospitalized 9 days in a French reference center for PWS where they were treated with a short course of intranasal OXT. A detailed clinical description of the population is shown in Table 1.

Table 1
Clinical characteristics of the population at birth and at inclusion.

Population (n = 18)	
Sex	
Male	10 (56%)
Female	8 (44%)
Genetic diagnosis	
Deletion	6 (33%)
mUPD	10 (56%)
Imprinting defect	2 (11%)
At birth	
Term (weeks)	39 (30; 42)
Prematurity (<37 weeks)	4 (22%)
Caesarean delivery	11 (61%)
Apgar 1 min	8.5 (3; 10)
Apgar 5 min	9.5 (5; 10)
Weight (SD)[a]	−1.2 (−2.5; 0.2)
Length (SD)[a]	−1.1 (−3.0; 0.9)
Head circumference (SD)[a]	−0.2 (−2.8; 2.4)
Tube Feeding (n/%)	16 (89%)
At inclusion	
Corrected age (months)	3.9 (0.8; 5.7)
Weight (SD)[a]	−1.4 (−2.7; 0.5)
Length (SD)[a]	−0.0 (−2.3; 0.1)
HC (SD)[a]	0.3 (−1.4; 2.4)
BMI (SD)[a]	−1.3 (−2.7; 0.6)
Tube feeding[b]	5 (28%)

Results are presented as median (minimum;maximum) or *n* = (%). Age is expressed as corrected age in premature babies. HC, head circumference.

[a] SD scores at birth were calculated according to Usher and McLean[9]. 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 in months. 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.

In addition to somatic exams, social withdrawal behavior and parent– infant interactions were assessed before and after treatment using the Alarm Distress Baby (ADBB) Scale and the validated Coding Interactive Behavior (CIB) Scale, respectively (Guedeney et al., 2013; Viaux-Savelon et al., 2014). The ADBB and CIB Scales were scored in a blinded manner on videos of feeding with father or mother taken before and after OXT administration by 2 experts.

2.2. Tools

The Alarm Distress Baby scale (ADBB) assesses social withdrawal behavior in children aged between 2 and 24 months, in the context of routine pediatric examinations or during specific psychological assessments. The ADBB Scale is a composite scale comprising 8 items with a score <5 indicating normal behavior. To facilitate the observation of the child's behavioral reactions, the observer, engages the child in social interactions through talking, touching and smiling. The scale comprises eight items including: lack of facial expression; lack of eye contact; lack of general level of activity; presence of self-stimulating gestures; lack of vocalizations; lack of rapidity of response to stimulation; lack of relationship with the observer; lack of attractiveness to the observer. Each item is rated from 0 to 4 resulting in 0 as the minimum and 32 as the maximum ADBB total score. The higher the ADBB score, the greater the signs of social withdrawal displayed by the infant. Validation studies of the ADBB in different countries have shown that infants with scores of 5 or above are at risk of adverse outcomes (Guedeney et al., 2013).

The Coding Interactive Behavior Infant and Feeding (CIB) (Feldman, 1998) is a well validated system for coding mother/infant interactions requiring trained observers (Feldman, 2007), validated in its French version (Viaux-Savelon et al., 2014), in various settings such as breast feeding (Silberstein et al., 2009) and skin-to-skin *Kangaroo* care (Feldman, Eidelman, Sirota, & Weller, 2002) and in various population (e.g. premature babies (Feldman and Eidelman, 2003). It is a global rating system of parent–child interaction that contains both micro-level codes and global rating scales. Each code is rated from 1 (a little) to 5 (a lot). Forty-two different codes are grouped into several interactive composites. Codes were averaged into composites that were theoretically derived, concerned with diverse aspects of early parent–infant relationships and showed acceptable to high levels of internal consistency. The French version has been validated and offers the same factorial distribution (Viaux-Savelon et al., 2014). Seven composite scores were used in the current study: (1) Parental sensitivity was the average of maternal acknowledgement of infant interactive signals, imitation and elaboration of the infant's behavior, gaze directed to the infant or joint activity, appropriate tone of voice/motherese, expression of positive and appropriate range of affect, resourcefulness in dealing with infant negative states, affectionate touch, supportive presence and infant-led interaction (the degree to which interactions were judged to be led by the infant, due to parental focus on the child needs and states rather than their own). (2) Parent intrusiveness was the average of parental inappropriate physical manipulation, parent overriding behavior (the degree to which mother disregards the infant's signals and interrupts the infant's ongoing behavior), parental negative affect/anger toward the baby, parental anxiety, parental criticizing of infant's behavior and parent-led interaction (the degree to which interactions were judged to be led by the parent's needs rather than the infant's needs, pace and agenda) (3) Dyadic reciprocity (synchrony) was the average of the parent's elaboration of the infant's vocalizations and movements, parental gaze directed to the infant, infant gaze directed to the parent or joint activity, verbal praises to the infant's behavior, affectionate touch and enthusiasm, infant vocalization/verbal output, warm and positive affect for both parent and child, dyadic adaptation- regulation and fluency of the interaction. (4) Negative dyadic status was the average of maternal negative affect/anger, the mother's hostility behavior, the child negative and labile affect, withdrawal from the environment, interactive constriction and tension. (5) Infant avoidance was the average of child negative and labile affect, withdrawal from the environment and avoidance behavior toward the parent. (6) Infant social engagement was the average of joint attention, child positive affect, affection to parent, alertness, fatigue, vocalizations/verbal output, initiation, competent use of the environment, creative-symbolic play and infant-led interaction. (7) Child state was the average of additional codes validated for feeding setting (Viaux-Savelon et al., 2014) and based on the Neonatal Behavioral Assessment Scale of Brazelton (Brazelton, 1983). It includes handling, appropriateness of infant state for feeding, ease to suck, gaze and vigil state adapted to feeding.

CIB composite scores were given after viewing the whole sequence of interaction with father or mother.

3. Statistical analysis

Data are presented for the whole population. 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 using Wilcoxon signed rank tests in the whole population. The score changes were compared using Kruskall–Wallis ranking tests when significant evolution was observed in the whole study group. Data analysis was per-

formed with Stata college Station, TX). P values ≤ 0.05 were considered statistically significant.

4. Results

4.1. ADBB scores

At baseline, the median ADBB score was 6.5, with 62% of the infants with an ADBB score above the threshold defining developmental risk (value of normal score, <5). Most infants with Prader Willy syndrom are clearly withdrawn. To our best knowledge, this study is the first to describe the level of social withdrawal behavior within Prader Willi Infants. The median score significantly improved for the whole group from 6.5 to 3.5 ($P = 0.005$), with 81% of infants after OXT treatment having an ADBB score below the threshold defining developmental risk. More specifically, we observed significant improvements on 4 of the 8 items: facial expression, from a median score of 1.0 to 0.0 ($P = 0.005$); eye contact, from 1.0 to 0.5 ($P = 0.043$); general level of activity, from 1.0 to 0.0 ($P = 0.028$); and relationships, from 1.0 to 0.0 ($P = 0.006$). Self-stimulating gestures are observed nor at baseline or after treatment, respectively 0 and 0 (1.000) (see Table 2).

4.2. CIB scores

Fig. 1 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 scoreof 2.47–3.08 ($P = 0.033$); dyadic reciprocity, 2.43–2.75 ($P = 0.009$); child social engagement, 1.91–2.50 ($P = 0.001$); and child state, 2.40–3.20 ($P = 0.002$).

Table 2
Scores of the ADBB composites in the population before and after OXT.

Variable	Population		
	N	Median	Min;max
Facial expression			
Before OXT	16	1	0;2
After OXT	16	0	0;2
P-value	*0.005*		
Eye contact			
Before OXT	16	1	0;3
After OXT	16	0.5	0;2
P-value	*0.043*		
General level of activity			
Before OXT	16	1	0;3
After OXT	16	0	0;2
P-value	*0.028*		
Self-stimulating gestures			
Before OXT	16	0	0;1
After OXT	16	0	0;2
P-value	*1.000*		
Vocalizations			
Before OXT	16	1	0;3
After OXT	16	1	0;2
P-value	*0.527*		
Response to stimulation			
Before OXT	16	1	0;2
After OXT	16	0	0;1
P-value	*0.248*		
Relationship			
Before OXT	16	1	0;3
After OXT	16	0	0;2
P-value	*0.006*		
Attractivity			
Before OXT	16	1	0;2
After OXT	16	0.5	0;2
P-value	*0.206*		

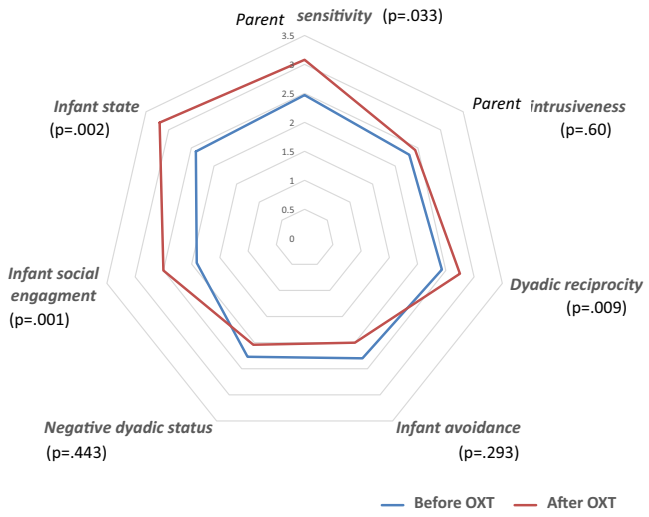

Fig. 1. CIB composite scores before and after OXT.

At baseline, the infants showed hypotonia, low expressiveness for positive or negative affects, fatigability and poor involvement in the relationship, as they were socially withdrawn. Parents tended to adapt to their child difficulties. However, the interaction was perturbed, tense, restricted and frequently intrusive with a forcing component that increased during the feeding situation. 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. They have a better global tonicity with better handling. These modifications helped the parents to be more sensitive. They are more aware to the child's social signals, elaborate more the children's signals. The dyad is less restricted and there is a best reciprocal exchange (dyad reciprocity). But the dyad stays tense.

5. Discussion

5.1. Relevance of the results in terms of early interaction

We document here the positive effects of OXT treatment on PW infant behavior and social engagement and on parent-infant interaction. These effects are reported here for the first time in human infants with pathology. Social withdrawal behavior was never assessed in the PW S before. The initial level of social withdrawal behavior in this sample is very high, compared to the level observed in community samples. The profile at the ADBB scale is specific with severe withdrawal and delay in response to stimulation without self-stimulating gestures.

We summarized in Fig. 2 the main results found before and after OXT. First, short course of repeated intranasal OXT administration improves oral feeding and social skills in infants with PWS. Second, despite OXT treatment is administrated to the child, the improvement is also observed on parent/infant interaction and parent's behavior. After OXT, the parent/infant dyad is less restricted and there is a better reciprocal exchange, thus engaging the dyad in a positive transactional spiral as well as optimizing feeding. This improvement is also supported by infant observation in gaze, holding, handling and social engagement.

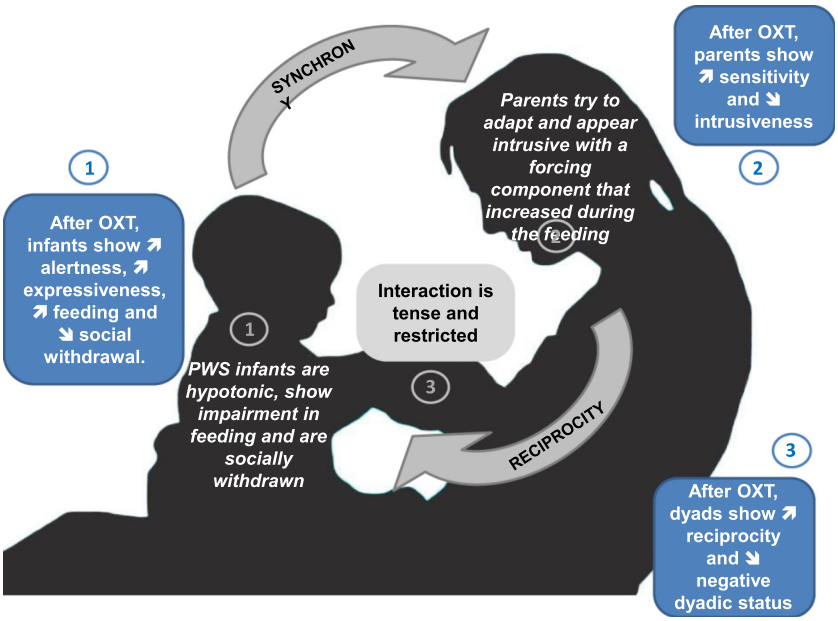

Fig. 2. Main results before and after OXT.

5.2. Motricity and sucking impact

The infant tonicity improvement has important consequence. As the infant is less hypotonic, he has better adjustment in parent's harms (handling) and his/her response to the tonic dialog with the parent improves the dyad reciprocity and synchrony. This motor synchrony has also an important impact on feeding efficacy. It is well known that this tonic dialog is particularly solicited during feeding. An abnormal sucking pattern was present at baseline for all infants and was normalized in 88% of them after OXT treatment (Tauber et al., 2017). This improvement of sucking is very important for parenthood sustain. Feeding his/her child is one of the most important ability expected from each parent toward his/her child (Teti et al., 2005). Indeed if the parent is able to feed alone (without nasogastric tube feeding), it gives him/her more confidence in their own capacity (Teti et al., 2005).

5.3. Synchrony impact

Improvement observed in ADBB and CIB ratings is coherent between the both scales. At baseline, parents are sensitive but in difficulty to perceive signals of their infant. Indeed infants' verbal or non-verbal signals are masked by their symptoms: hypotonia, poor facial expressivity, low level of engagement and initiatives toward the partner. Interaction is trapped, emotionally restricted, tense and sometimes intrusive. Feeding disorder induces easily this intrusion component with food forcing when the infant has to gain weight. Self-stimulating gestures (ADBB item) are observed nor at baseline or after treatment, as we expected. This item is more usually perturb in autism or severe neglectness.

After OXT treatment, infants were more alert, less fatigable, more expressive, and had less social withdrawal and better eye contact. They initiated mutual activities and were more engaged in relationships through gaze, behavior, and vocalizations. The relationship is more leaded by the infant.

It is likely that improved facial expression, eye contact, general level of activity and relationships offer to the infant the ability to communicate better with his/her parent and to be better understood by him/her as illustrate through better parental sensitivity and dyadic reciprocity. These modifications helped the parents to be more sensitive. The parent/infant dyad becomes less restricted with more reciprocal exchange, thus engaging the dyad in a positive transactional spiral (Sameroff, 2009) as well as optimizing feeding. The dyad is more expressive although parents could keep some intrusive behavior. Modalities of interaction constructed in the first months of the infant life would be difficult to remove and the baby keeps some symptoms.

In term of synchrony we wish to add some qualitative comments. We believe that the feeding being more successful, parents are less anxious, more open to change. The range of their affects is widened and they show more resources and creativity to engage the child. Also at baseline vocalizations were nearly none. After OXT, infant express sometimes for the first time vocal communication both positive and negative. We noticed than some parents were perturbed by this change, particularly by emergence of cry or opposition.

5.4. Oxytocin role

The role for OXT in the initiation and maintenance of affiliative bonds and parental repertoire has been elucidated in animal research that spans several decades (Insel, 2010) and more recently also in humans (Carter, 2014). Similarly, the oxytocinergic system in the brain and periphery has been suggested to underlie the cross-generation transmission of parenting in humans (Feldman, 2012) For example, a single-dose of OXT administered to a parent was found to enhance the parent's physiological, hormonal and behavioral readiness for social interaction with the infant, but at the same time to modulate the infant's readiness for social engagement, as reflected also in the infant's salivary OXT increase (Weisman et al., 2012)

However, the specific human carer's cues that are affected by OXT, which may be central to this affiliative transmission process, remain largely unknown. Studies on the attachment phenomenon in animals show that motion and vocalization are key visual and auditory inputs for the offspring (Lorenz, 1935; Falk 2004). Likewise, motion generally attracts human infants'attention (Tronick, 1972). For instance, during chasing, acceleration seems to be a key parameter to draw infants' attention (Frankenhuis et al., 2013), and speed of others' movements may automatically influ-

ence the observer's action (e.g. the timing of movement execution) Watanabe, 2008). Similarly, recent studies showed the OXT-induced suppression of cortical activity at the alpha/mu and beta bands when biological motion is viewed (Perry et al., 2010), implying heightened sensitivity towards biological versus non-biological motion (Keri and Benedek, 2009) In addition, OXT administration modulated social distance between males and females during interactions (Scheele et al., 2012) and mothers' speech stimulated OXT release in girls (Seltzer et al., 2010). Finally, OXT administration shapes parental motion characteristics during parent/infant interaction (Weisman et al., 2013). Taken together, these findings suggest that proximity and movement might be affected by acute OXT intervention, but also that parental vocalization is another nuanced feature that affects the OT system in humans. OXT has also direct implication on motor function. It is likely that OXT improves oral motor function of the face and head, including the larynx and pharynx.

PWS's early genetic diagnosis, which is now realized in the first months of life and sometimes in utero, (Butler, 2017) offers a unique opportunity for early treatment as well as psychomotor symptoms, nutritional symptoms than interactions disorders. The natural outcome of the Prader-Willi syndrome is quite gloomy, with early anorexia turning into bulimia, with social withdrawal behavior leading to clear to severe mental retardation and to behavioral difficulties, increasing around adolescence.

The Prader Willi symptoms perturb by themselves the synchrony between parents and their child as we can see in early prematurity (Feldman and Eidelman, 2003). Environmental factors come to raise this perturbation particularly the emotional state of the parents. All the factors who can improve the child expression or parental sensitivity allow to improve synchrony in the dyad and by this way decrease impact on orality disorder or behavior disorder that are often describe in the second childhood for this pathology. OXT impact on child withdrawal and child expression has an important role to play for this specific pathology associated to child psychiatrist guidance to limit the impact of over-added factors which exacerbate initial symptomatology.

6. Conclusion

Dyssynchrony can be induced by children pathology as well as parental pathology. In both cases, this can have emotional and developmental impact. The Prader-Willi paradigm shows us the necessity to sustain early parents-child relationship. OXT treatment shows in a very short period of time how the improvement of child ability (gaze, tonicity, suck, vigil state) can impact in the same time the parental state and the synchrony of the dyad in a positive transactional spiral (Sameroff, 2009).

Acknowledgments and tribute

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Tribute to Dr Elisabeth Aidane, MD, who died this week. She was one of the pioneers of 0-3 unit of Pitie Salpetrière Hospital and she introduced several members of this team to perinatal clinic and early psychopathology. She never stopped to teach us and to open doors to collaborations and friendship.

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