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Review of the literature

The effects of oxytocin on social cognition in borderline personality disorder

Effets de l'ocytocine sur la cognition sociale dans le trouble de personnalité borderline

A. Servan [a], J. Brunelin [b,c,d,e], E. Poulet [a,b,c,d,e,*]

[a] *Groupement hospitalier centre, pavillon N, service de psychiatrie des urgences, hospices civils de Lyon, 69003 Lyon, France*
[b] *Inserm U1028, CNRS UMR 5292, ΨR2 Team, Lyon Neuroscience Research Center, 69000 Lyon, France*
[c] *University of Lyon, 69000 France*
[d] *University of Lyon 1, 69000 Villeurbanne, France*
[e] *Centre hospitalier Le-Vinatier, 69678 Bron, France*

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ABSTRACT

Introduction. – Deficits in social cognition and interpersonal difficulties are key features in borderline personality disorder. Social cognition refers to the function of perceiving and adequately dealing with social signals, leading to the establishment and maintenance of healthy and positive social relationships. Evidence suggests that oxytocin (OT) may improve social cognition and human social behavior. Recently, several studies have highlighted the beneficial effects of oxytocin in several psychiatric conditions involving social cognition deficits such as schizophrenia, autism or social phobia. However, despite growing interest, the effects of oxytocin in patients with borderline personality disorder are far from being clearly demonstrated.

Objective. – The objective of this work was to review and discuss studies investigating the interest of oxytocin in alleviating social cognition deficits in patients with borderline personality disorder (recognition of emotion, trust and cooperation, affective and cognitive empathy, emotional expression and social problem-solving).

Method. – A systematic review of the literature was conducted up to September 31, 2016 on the Pubmed, Science direct, Medline and Scopus databases using "borderline personality disorder" and "oxytocin" as keywords. To be included, studies were to include patients with borderline personality disorder; to investigate social cognition and to investigate the effect of oxytocin on social cognition in patients with TPB.

Results. – The initial search yielded 52 articles. Among them, 11 studies were selected according to the PRISMA criteria. The effect of oxytocin on social cognition in patients with borderline personality disorder was mainly investigated in relation to recognition of emotions and trust and cooperation. We did not find any studies investigating the effect of oxytocin on affective and cognitive empathy, emotional expression or social problem-solving abilities. In patients with borderline personality disorder, oxytocin had a beneficial impact on recognition and discrimination of emotions and on hypervigilance towards social threats. However, oxytocin could hinder trust and cooperation.

Conclusions. – These data lead us to consider oxytocin as a treatment for emotion recognition deficit and hypervigilance towards social threats in borderline personality disorder. A beneficial effect of oxytocin of this nature may be obtained only in patients without deficits in trust and cooperation because of a risk of aggravating relational instability. There was no current evidence for the interest of oxytocin in enhancing affective and cognitive empathy in borderline personality disorder. Further studies are needed to evaluate the clinical interest of combining oxytocin with psychotherapeutic approaches such as dialectical behavioral therapy or mentalisation-based treatment.

* Corresponding author at: Groupement hospitalier centre, pavillon N, service de psychiatrie des urgences, hospices civils de Lyon, Lyon, France.
E-mail address: emmanuel.poulet@chu-lyon.fr (E. Poulet).

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RÉSUMÉ

Objectif. – L'objectif de cette revue est d'évaluer l'intérêt de l'ocytocine sur les différentes dimensions de la cognition sociale qui sont altérées dans le trouble de la personnalité *borderline* : la reconnaissance des émotions, l'empathie affective, l'expression des émotions, l'empathie cognitive, la résolution des problèmes sociaux et la confiance et la coopération.
Méthode. – Revue systématique de la littérature des banques de données informatisées Pubmed, Science direct, Medline et Scopus avec les mots clés : « borderline personality disorder » et « oxytocin ».
Résultats. – Parmi les 52 études retrouvées dans la littérature, 11 études ont été retenues. Ces études montrent que l'ocytocine est efficace sur le déficit de reconnaissance des émotions et sur l'hypervigilance à la menace sociale chez les patients présentant un trouble de la personnalité *borderline*. Cependant, l'ocytocine peut également aggraver la difficulté à faire confiance et à coopérer avec un partenaire social. Nous n'avons pas retrouvé d'études sur l'expression des émotions, sur l'empathie affective et cognitive et sur la résolution des problèmes sociaux.
Conclusions. – Ces données nous amènent à envisager l'utilisation d'ocytocine pour traiter le déficit dans la reconnaissance des émotions et l'hypervigilance à la menace sociale chez les patients avec un trouble de la personnalité *borderline*. Cependant, l'ocytocine ne devrait pas être administrée aux patients avec un déficit dans la confiance et la coopération au risque d'aggraver leur instabilité relationnelle.

Mots clés :
Trouble de la personnalité *borderline*
Ocytocine

1. Introduction

Borderline personality disorder is a prominent clinical disorder with poor prognosis, characterized by high mortality, in particular by suicide (up to 10% of patients die by suicide), and frequent hospitalisations [1]. It affects 1% to 6% of the non-clinical population, 10% of the psychiatric population, and 20% of patients hospitalised in a psychiatric facility [2].

Since it was first described by Stern in 1938, instability in interpersonal relationships appears as a baseline characteristic of borderline personality disorder. Among patients with BDP emotional lability, impulsiveness, relational difficulties and disturbances in identity and cognition are frequently observed [3]. In its diagnostic criteria, the recent version of the DSM (DSM-5) also includes efforts deployed to avoid abandonment, the repetition of self-harm behaviours, the chronic feeling of emptiness and difficulty controlling anger [4]. These criteria can be conceptualised in three fundamental dimensions corresponding to instability in interpersonal relationships, impulsiveness and affective dysregulation [5]. Among subjects exhibiting borderline personality disorder, social situations appear as powerful triggers for emotional excitation and affective instability [6] leading to impulsive adaptative behaviours [7]. In addition to the theoretically central role of disordered interpersonal relations in borderline personality disorder, sufferers describe altered interpersonal functioning as being significantly problematic [8].

Whatever the international classification used, deficits in the field of social cognition and in interpersonal relations are central to diagnosis of borderline personality disorder. The phrase "social cognition" refers to the ability to perceive and adequately process the social signals that enable quality social relationships to be established and maintained. The difficulties observed in the different areas of social cognition in borderline personality disorder have been classified in six broad domains in this area of research: recognition of emotions, affective empathy, the expression of emotions, cognitive empathy, social problem-solving, and trust and cooperation.

Concerning performances in the recognition of emotions, certain studies demonstrate a deficit in the recognition of negative emotions in borderline personality disorder [9,14], while others conclude to excessive recognition of negative emotions such as fear [10] or anger [9,10]. Regarding affective empathy, there are studies that report either a deficit corresponding to difficulty feeling the emotions of others [11,12], or else excessive contagion of emotions [13]. The expression of emotion in these subjects could be more difficult to read [4] with a tendency to more readily reflect negative facial expressions [15]. In addition to this, several authors have described a deficit in cognitive empathy among borderline personality disorder patients [11–13,16], or more negative assessments of the other person [8]. It may be that borderline personality disorder patients use more passive [17] and less relevant [18] means to solve social issues. Finally, studies assessing trust and cooperation among these patients report deficits in these two areas [19].

Today, psychotherapy is the recommended first-line treatment in borderline personality disorder [20]. Certain pharmacological treatments targeting symptoms are also classically used, but with fairly small effect on interpersonal instability and the overall severity of borderline personality disorder [21]. This lack of efficacy often results in the excessive use of medication [22] despite inadequate proof of its efficacy [23]. This information led us to consider new, specific therapeutic approaches so as to improve care provision in borderline personality disorder, and interpersonal difficulties appear as a worthwhile target. Interpersonal symptoms are indeed slow to recede, with 15 to 20% of individuals with borderline personality disorder presenting these symptoms at outset failing to improve after 10 years' follow-up [24], which has long-term consequences on social functioning [25]. Disordered interpersonal functioning thus has an important role in the prognosis of borderline personality disorder.

It is recognised today that oxytocin (OT) produces effects on social cognition and on human social behaviours. Oxytocin is a neuropeptide synthesised in the magnocellular neurons of the paraventricular and supraoptic nucleus of the hypothalamus. This neuropeptide is then transported to the posterior pituitary gland where it is released [26]. Several studies suggest that there are oxytocin receptors in the brain areas that are closely linked to social behaviours, such as the limbic structures [27]. Oxytocin, often known as the "social hormone", is at present generating considerable enthusiasm for its potential role in the treatment of certain psychiatric disorders [28], and in particular, those implicating disorders in social cognition such as autism, schizophrenia and social anxiety, producing results that are often favourable [29]. In this sense, borderline personality disorder could provide an interesting target. Bertsch et al. compared oxytocin levels in female patients with borderline personality disorder with those of healthy subjects. In the clinical group, they found plasma concentrations of oxytocin that were below those in the healthy subjects [30]. Likewise, lower levels of plasma oxytocin have been found in

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schizophrenia, and could be negatively correlated with the seriousness of psychotic symptoms [31]. Thus, borderline personality disorder subjects could present neurochemical changes in the oxytocin system, and these anomalies could be associated with a large part of the symptom profile in the disorder. Correction via oxytocin supplementation could provide a new therapeutic approach.

In the light of this data, social cognition disturbances in borderline personality disorder could be potential clinical targets for oxytocin. This literature review aimed to explore the interest of oxytocin for the different dimensions of social cognition affected in borderline personality disorder.

2. Methods

A systematic review of the literature was performed via exhaustive documentary search on PubMed and Scopus databases up to September 2016, using the key words "borderline personality disorder" and "oxytocin". A second search was performed on Medline and Science Direct using the same keywords. This database search was completed by a manual search for references quoted in the articles retained so as to assemble all articles on the subject in hand.

Only articles on the use of oxytocin in borderline personality disorder were included. Literature reviews were included, but with systematic ascertainment of the validity of data in the original articles. No study was excluded based on year of publication, language, or study design.

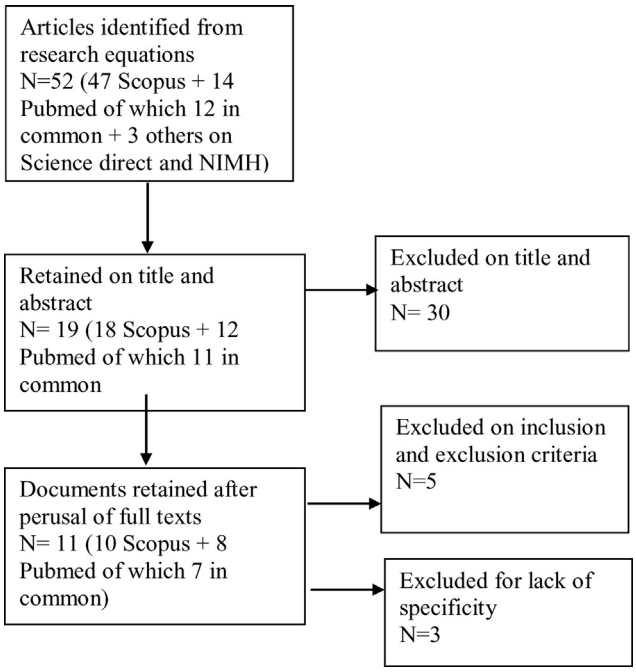

Fig. 1. Flowchart.

3. Results

Article selection was conducted on the results of the PubMed and Scopus database searches, while the other databases provided three further articles. Following the search, 19 articles were selected based on title and abstract. All these articles were perused, using PRISMA scoring criteria to identify the articles with the highest scientific standards [32]. Only studies including borderline personality disorder patients, measuring performances in an area of social cognition and discussing the effects of oxytocin on the parameters of social cognition in borderline personality disorder were retained. After perusal of the full texts of these studies, 14 met the criteria. Three studies on the effects of oxytocin in borderline personality disorder were removed on account of their lack of specificity on the subject. Among articles dating from before 2015, we retained those cited at least 5 times, and the most recent reviews. In all, 11 articles were finally included. The selection procedure is detailed in the flow diagram in Fig. 1.

We now propose to describe and discuss the main results derived from the literature review. This concerns the data available on the effects of oxytocin on social cognition deficits in borderline personality disorder. In view of the results, we will then discuss the interest of oxytocin in the treatment of these deficits.

3.1. The effect of oxytocin on recognition of emotions in borderline personality disorder

In borderline personality disorder, it has been shown that when reflex eye movements are too numerous and too rapid and oriented towards eyes expressing anger, oxytocin normalised the speed and number of eye movements [33]. Thus, oxytocin could reduce hypersensitivity to social threats. This effect could help reduce reactivity to stress, to hostility or to anger, and the aggressive reactive behaviours that result from it [34].

Certain patients presenting borderline personality disorder appear to exhibit avoiding behaviours when viewing angry faces, and this reaction could be neutralised by oxytocin [34]. Thus, oxytocin could provide better confrontation with anger-related stimuli, and better recognition of that emotion.

It thus seems that patients with borderline personality disorder could benefit from the administration of oxytocin on account of its effects on the recognition of facial emotions [29], whether the problem is a deficit or conversely hypersensitivity towards threatening emotions.

From a neurophysiological viewpoint, under oxytocin, a decrease in the activation of the amygdala is observed, which could reduce these subjects' attentional bias towards threatening social indices [33]. It can be noted that oxytocin reduces the activation of the posterior amygdala, probably the basal nucleus [33], which appears to be involved in the orientation of attention towards negative facial expressions in the visual periphery and towards sites that are socially relevant in the visual field [35].

We found no information on the effects of oxytocin on the insula or the anterior cingulate cortex in borderline personality disorder, areas that are thought to be involved in the processing of emotionally charged facial stimuli [36] and in selective attention respectively.

3.2. The effect of oxytocin on affective empathy in borderline personality disorder

Whether in the clinical domain or in the domain of neuropsychology, no study to our knowledge has been conducted to assess the effects of oxytocin on affective empathy in borderline personality disorder.

3.3. The effect of oxytocin on the expression of emotions in borderline personality disorder

Whether in the clinical domain or in the domain of neuropsychology, no study to our knowledge has been conducted to assess the effects of oxytocin on the expression of emotions in borderline personality disorder.

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3.4. The effect of oxytocin on cognitive empathy in borderline personality disorder

Whether in the clinical domain or in the domain of neuropsychology, no study to our knowledge has been conducted to assess the effects of oxytocin on cognitive empathy in borderline personality disorder.

3.5. The effect of oxytocin on the social problem-solving in borderline personality disorder

Whether in the clinical domain or in the domain of neuropsychology, no study to our knowledge has been conducted to assess the effects of oxytocin on social problem-solving abilities in borderline personality disorder.

3.6. The effect of oxytocin on trust and cooperation in borderline personality disorder

Several studies explored the effects of oxytocin on trust and cooperation in borderline personality disorder. They showed that oxytocin did not improve trust, and conversely, that it could generate a deterioration in trust [37,38]. This effect appeared to be independent from the action on reactivity to social stress, which could be reduced by oxytocin [39]. In a study assessing non-verbal communication, pro-social behaviours in social interactions were found to be reduced under oxytocin [40].

Likewise, the administration of oxytocin was reported to result in altered cooperation with social partners and an absence of response to hypothetical cooperation on the part of the partner [37]. Under oxytocin, patients with borderline personality disorder could be more likely to be guided by the desire to punish their social partner [37].

4. Discussion

This work is the first exhaustive review of the literature aiming to study links between social cognition deficits in borderline personality disorder and oxytocin. Article selection was performed according to the international PRISMA criteria so as to ensure an analysis of relevant information derived from studies with satisfactory levels of proof. This review highlights several results.

In case of deficit in the recognition of facial emotions, the administration of oxytocin could improve the recognition of anger by deactivating the avoiding reaction when confronted with faces expressing that emotion. Oxytocin could also reduce hypervigilance towards negative emotions by reducing the focus of gaze around the area of eyes expressing a threat. In borderline personality disorder, the efficacy of oxytocin on hypervigilance towards social threats could be mediated by its action on the amygdala, reducing its hyperactivation in the face of negative emotions. Its impact on other brain areas involved in the recognition and identification of emotions have not been studied in borderline personality disorder.

To our knowledge, no study has set out to assess the effects of oxytocin on cognitive empathy in borderline personality disorder. However, studies on healthy volunteers, which found that oxytocin could improve abilities for cognitive empathy [41] via increased attention [42] and social memory [41], suggest a possible beneficial effect in borderline personality disorder.

Finally, studies assessing the efficacy of oxytocin on trust and cooperation suggest alterations in these components. Under oxytocin, borderline personality disorder patients appear to be guided by the desire to punish their social partners.

To our knowledge no study has been performed on the effects of oxytocin on the expression of emotions or on social problem-solving abilities, whether in the general population or in borderline personality disorder.

Thus, the effects of oxytocin in borderline personality disorder appear complex and fairly ambivalent, in line with the results of existing studies [43–45]. Given the heterogeneous nature of social cognition disorders in borderline personality disorder, reflecting the clinical heterogeneity of these patients, a thorough exploration of social cognition on an individual basis in order to assess the different parameters involved could be a relevant requirement before any prescription of oxytocin.

There are several limitations to this review of the literature. First of all, the studies assessing the efficacy of oxytocin among borderline personality disorder patients only explored certain areas of social cognition. The effect of oxytocin on emotional expression or the social problem-solving in particular, has been explored neither in borderline personality disorder nor among healthy volunteers. Thus, the effects of the administration of oxytocin cannot as yet be apprehended for these dimensions.

The oxytocin administration protocols appear very variable from one study to another, which implies the need to harmonise conditions for the use of oxytocin in future studies. For exogenous usage, the intranasal route provides a direct pathway to the brain [46]. Intranasal administration of oxytocin at a dose of 24 to 32 IU has become the norm in human studies, and this could be relevant in clinical usage [47].

In order to determine the factors that influence the effects of oxytocin [48] and define target cognitive phenotypes for this therapeutic option in borderline personality disorder, we looked at individual and contextual factors appearing in the studies considered.

In borderline personality disorder, it has been suggested that children growing up in a traumatic or debilitating environment could have more intuitive emotional assessments than others, translating into hyperactivation of the amygdala and hypoactivation of the mirror neurones [49]. This type of activation has been observed in borderline personality disorder in tasks involving affective empathy. The effect of oxytocin on affective empathy in the general population is also thought to be modulated by the style of attachment of the individual [50] – individuals with poorly secure attachment may benefit less from the effects of oxytocin on affective empathy [47]. This data therefore suggests that oxytocin might not be effective in improving affective empathy among patients with borderline personality disorder presenting an attachment disorder.

In borderline personality disorder, an unstable attachment style could also lead to greater mistrust and poor cooperation [51]. It can also be noted that in case of anxious attachment in childhood, oxytocin appears to reduce cooperation and trust in others [37].

Attachment disorders could thus be factors that aggravate different social cognition anomalies in borderline personality disorder, and also factors limiting the efficacy of oxytocin on these same anomalies. Among borderline personality disorder patients, it should be noted in this respect that 50 to 80% are thought to present an attachment disorder [52]. This could lead us to question the interest of oxytocin in borderline personality disorder, given the attendant risk of worsening these individuals' relational instability.

Borderline symptoms as a whole could be important modulating factors to be taken into account, because of the stress they generate. Unoka et al. noted that interpersonal and cognitive symptoms could lead to variations of 33% in the sums of money invested in a trust game, suggesting a link between reduced trust and stress linked to the intensity of borderline personality characteristics, such as difficulties in interpersonal relations [19]. Likewise, oxytocin could have differential effects among borderline personality disorder patients according to their degree of chronic interpersonal insecurity [37], reducing trust and the likelihood of cooperation all

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the more markedly when their scores for relational anxiety and fear of rejection are higher [37]. This data is in favour of an absence of efficacy of oxytocin on trust and cooperation in presence of stress factors often found in borderline personality disorder.

Among the frequent symptoms in borderline personality disorder, emotional hyper-excitation could underpin failure to recognise negative emotions presented in prolonged or intense manner [53]. Emotional hyper-excitation could also lead to the acceleration of reflex eye movements and their orientation towards the eyes of angry faces [33], thus favouring fixation on threatening social indicators. In case of hyper-reactivity to negative emotions (marked depressiveness or marked hostility), oxytocin could act by reducing the activation of the amygdala, thus reducing the perception of threat [33]. In addition, in borderline personality disorder, affective empathy could be markedly reduced in situations that are emotionally distressing or in case of strong emotional reactions towards others [10], which shows the potential impact of emotional dysregulation on affective empathy. Emotional dysregulation has also been linked to deficits in cognitive empathy [10] and hypermentalisation [54].

Thus, emotional dysregulation, and in particular emotional excitation, appears as a factor that aggravates several dimensions of social cognition in borderline personality disorder. It could favour the efficacy of oxytocin in the alleviation of hypersensitivity to social threats observed in borderline personality disorder.

Bartz et al. reported efficacy of oxytocin on cognitive empathy in the general population only when the subjects presented social deficits [50]. Borderline personality disorder patients are thought to present deficits for several parameters of social cognition, which appears to be in favour of efficacy of oxytocin in cognitive empathy deficits.

Finally, the social context appears to have an impact on the effects of oxytocin on trust and cooperation. It seems that oxytocin improves neither reliability, nor trust nor cooperation among borderline personality disorder patients when their partners have been reliable, worthy of trust or cooperative in the past [37]. Conversely, oxytocin could increase cooperation solely when the partners are seen as non-cooperative [37].

5. Conclusion

This literature review shows that the administration of oxytocin is worth envisaging to treat deficits in the recognition of anger and hypersensitivity to social threats among patients with borderline personality disorder, as a result of its action in the recognition of facial emotions. Given the frequency of attachment disorders, fear of rejection and relational anxiety in borderline personality disorder, its use does however risk aggravating the lack of trust and poor cooperation observed in this disorder, thus constituting a major obstacle to its use among these patients. The indication for oxytocin in borderline personality disorder should thus be restricted to use with patients presenting solely an anomaly in the recognition of facial emotions, characterised by hypersensitivity to social threats. The absence of data on the usefulness of oxytocin on the two domains of empathy, on the expression of emotions, and on the social problem-solving abilities in borderline personality disorder precludes conclusions on its usefulness in these areas.

In addition, these results provide a warning as to the variability of the behavioural effects of oxytocin according to individual and contextual factors. Thus, oxytocin is not the miracle drug favouring relationships independently from context, personality and the patient's personal history. There is thus a need for further study to compare social cognition in the different subgroups of borderline personality disorder and the usefulness of oxytocin within these subgroups according to their individual and contextual features.

Finally, oxytocin can, in no way, be considered as a treatment for all the difficulties encountered by borderline personality disorder patients. But, in a RDoC type approach, it could provide a possible line of research for certain trans-nosographic dimensions, and thus find applications in different pathologies characterised by social cognition disorders, such as the emotional recognition deficits found in schizophrenia and autism. It is a therapeutic approach with some interest, which might be used in association with existing care procedures such as psychotherapy, as suggested by Brüne, Heinrichs and Domes or Amad et al. [43,45,55]. A recent meta-analysis looked at the effects of psychotherapeutic techniques in the treatment of borderline personality disorder [56]. The authors report a significant effect on different dimensions of the disorder (self-harm, suicide, general psychopathology) but the effects seem to be slight, and unstable over follow-up. The concurrent use of oxytocin and tailored psychotherapy programmes used in this indication, such as the dialectic behavioural therapy developed by Marsha M. Lineham or Bateman's therapy based on mentalisation, provide interesting perspectives that need to be evaluated experimentally.

Disclosure of interest

The authors declare that they have no competing interest.

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