

Title: Treating Borderline Personality Disorder with Oxytocin: An Enthusiastic Note of Caution
Commentary to Servan et al. *The Effect of Oxytocin in Borderline Personality Disorder*

Title: Traiter le trouble de la personnalité borderline avec l'ocytocine: un bémol enthousiaste
Commentaire à Servan et al. *Effets de l'ocytocine dans le trouble de la personnalité borderline*

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Dans cette revue de la littérature, Servan et collègues proposent une analyse nuancée des résultats d'études cliniques examinant les effets de l'administration de l'ocytocine sur les processus de cognition sociale dans le trouble de la personnalité borderline (TPB). Cette revue de la littérature tombe à point nommé, car elle permet d'apprécier les effets positifs du neuropeptide tels qu'observés dans des protocoles de recherche clinique expérimentale, tout en exposant les effets potentiellement iatrogènes de l'administration de l'ocytocine sur la stabilité relationnelle, la confiance et la coopération chez le sujet avec TPB. Nous relevons certaines limitations du champ actuel des connaissances qui doivent être prises en compte avant d'imaginer la possibilité d'un usage thérapeutique de l'ocytocine dans le contexte du TPB. Tout d'abord, comme le soulignent Servan et collaborateurs, de nombreux processus de cognition sociale, comme l'empathie et l'expression émotionnelle, n'ont à ce jour pas fait l'objet d'étude clinique. De plus, les études cliniques expérimentales utilisent des stimuli dont la faible validité écologique limite toute forme de généralisation aux difficultés de cognition sociale dans le TPB, qui ne s'expriment pas à la façon d'un déficit, mais bien d'un dérèglement contextualisée aux situations relationnelles et sociales à lourd dosage affectif. En menant des recherches scientifiques mettant en lumière l'effet des nombreux paramètres susceptibles de moduler l'impact de l'ocytocine dans le TPB, notamment ce qui concerne la comorbidité psychiatrique, les schémas d'attachement, ainsi que la susceptibilité différentielle déterminée par le profil génétique du sujet, l'avenir nous informera sur les conditions propices conférant une valeur additive significative de l'ocytocine aux psychothérapies empiriquement fondées.

In their review, Servan et al. provide a timely and critical appraisal of the literature linking the effects of oxytocin (OT) on social cognitive functions in Borderline Personality Disorder (BPD) (Servan, Brunelin, & Poulet). Their review is useful in many ways. First, the authors survey the main results of interest, namely the beneficial effect of OT reported on emotion recognition performances in the laboratory, as well as the regulating effect of OT on hypervigilance to experimentally-induced social threat. Furthermore, unbeneficial effects of OT on trust and cooperation paradigms have been reported in BPD. Servan et al. thus faithfully present the inconsistent nature of the results of this topic, or as they formulate it, the “*complex and ambivalent*” effect of oxytocin on social cognition in BPD. Second, the authors usefully direct attention to additional social cognitive processes that would be worthwhile to examine in relation to oxytocin in BPD, such as cognitive and affective empathy, expression of emotions and social problem-solving. The scarcity of research on such key processes further warrant restraint in the therapeutic usage of this neuropeptide in BPD, if only because these key social cognitive mechanisms have yet to be thoroughly investigated. In their discussion, Servan et al. raise the issue of potential factors moderating the effects of oxytocin on social cognitive processes in BPD, especially trauma history, post-traumatic stress disorder, and attachment style. More critically perhaps, these intervening moderating factors must alert to potential iatrogenic effects of therapeutically administering OT in this population, where a negative therapeutic impact such as increased relational instability may ensue.

In light of these careful observations and heterogeneity of the results relating the effects of OT on social cognition in BPD, Servan et al.’s statement at the outset of their abstract’s conclusion might appear somewhat surprising: “*These data lead us to consider oxytocin as a treatment for emotion recognition deficit and hypervigilance towards social threats in borderline personality disorder*”. The statement may not be necessarily wrong, but stated as a concluding remark, we feel it may be somewhat premature. Indeed, upon reading their review, any clinician would be warranted to wonder whether administering OT, while increasing the patient’s emotion recognition accuracy and decreasing hypervigilance to threat, may indeed increase relational instability, or negatively impact trust and cooperation? Fundamentally, we agree with Servan et al. that upon further research, OT may reveal to be a helpful pharmacological agent integrated in personalized medicine protocols for BPD. However, for the reasons detailed below, we predict that this day lies somewhere within the short to midterm future.

The first reason for caution pertains to the nature of stimuli employed in the reviewed studies, and specifically, the degree to which studies are “naturalistic” enough to simulate real-life performances in participants with BPD. In the facial emotion recognition paradigms reviewed by Servan et al., the stimuli consist of standardized, often static pictures of unambiguous facial emotional expressions, portraying individuals unknown to the participant. Administering OT may increase the salience of facial emotional cues to stimuli the participants may have otherwise processed only superficially; however, the BPD symptoms putatively induced by faulty emotion recognition almost exclusively occur with “facial stimuli” of significant others expressing ambiguous emotions, in real-life, affect-laden situations. Moreover, it appears that hypervigilance, through influence on visual scanning (Bertsch, Schmidinger, Neumann, & Herpertz, 2013), can generate “hyper-mentalization” (Sharp et al., 2013), that is, an

interpretative style that goes far beyond the available evidence whereby mental states are inferred with unwarranted levels of certainty. Indeed, as far as emotion recognition is concerned, recent reviews suggest that individuals with BPD may sometimes outperform controls in laboratory tasks (Lynch et al., 2006). In this context, before concluding to the beneficial *therapeutic* effects of OT on emotion recognition in BPD, further research using dynamic, naturalistic stimuli (Morosan et al., 2017), should yield additional information on the robustness of emotion recognition in BPD with or without OT. The same should be performed with regards to the hypervigilance phenomena, as it may well be the case that OT administration does not carry beneficial effects when processing stimuli that trigger high levels of arousal, like for example the participant's boss's or ex-lover's portraits... The point here is that contrary to some depictions in the literature, individuals do not suffer from "deficits" in emotion recognition, but rather, are likely victims of their social cognitive lability in the face of affective arousal and/or poor emotion regulation (Badoud et al., 2017). In such instances, factors instantiating individual differences in response to OT, which include genetic profiles (Olofsdotter, Aslund, Furmark, Comasco, & Nilsson, 2017), will critically inform the ambition set out for OT as a therapeutic agent. At the neurobiological levels, future work will benefit from examining OT effects in the context of its interaction with neuromodulators linked to stress (i.e. cortisol; (Fragkaki, Cima, & Granic, 2018) and salience (i.e. dopamine; (Shamay-Tsoory & Abu-Akel, 2016), which critically modulate social cognitive processes in BPD (Luyten & Fonagy, 2015).

To recapitulate, Servan et al. provide an important review of the literature on OT effects in BPD social cognitive processing, characterizing the state of the literature as still searching for reproducible patterns of results, and areas that require further investigation. In relation to the early stages of this field of research, we argue that it is premature to currently view OT outside the confines of basic and clinical research. The studies to date point to both methodological and contextual factors that motivate both naturalistic studies as well as more basic neuroscience studies before they can legitimately inform new treatment protocols. In this context, we would not advise pairing OT administration and empirically validated treatments such as dialectic or mentalization based therapies outside of clinical trial methodologies. Critically, basic knowledge on how OT interacts with key genetic polymorphisms and relevant neuromodulators in the brain is still missing. Finally, because the response to OT administration may depend on individual differences in the ability to maintain social boundaries (Leppanen, Ng, Tchanturia, & Treasure, 2017), OT's action will inevitably reveal to be complex and ambivalent in the ways it activates or de-activates social cognitive processes, with potentially adaptive but also maladaptive effects.

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