

Intranasal Oxytocin and Social Interactions in 5 Patients With High-Functioning Autism Spectrum Disorder

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The diagnostic category of autism spectrum disorder (ASD) refers to a variety of conditions, sharing the common core of persistent deficits in social communication and social interaction across multiple contexts.” These conditions can be thought as a continuum, ranging from a pole with severe delay in cognitive, social, and emotional development to a pole defined as high-functioning autism spectrum disorder (HF-ASD), which implies a regular development of cognitive abilities, with a selective impairment in understanding and responding to social cues (APA, 2013).[1] the etiology of ASD is still not clear, recent models underlined a key role for gene-environment interaction; within genes implicated in the etiology of ASD, the oxytocin (OXT) receptor gene seems to be specifically implicated in the social deficits seen in patients with HF-ASD. Despite the growing literature on OXT and ASD, [2,3] up to date, no studies have observed the effect of intranasal administration of OXT on social abilities of patients with HF-ASD in a real group setting, which is one of the most common settings where social abilities need to be used and where group interactions might serve as cues for social abilities. The aim of this study was to qualitatively observe the effect of a single intranasal administration of OXT on social abilities in patients with HF-ASD, both assessed individually and in a group setting. Five patients diagnosed with HF-ASD, according to Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria, who have participated in the same group therapy once a month for 7 years, have been recruited. They all signed an informed consent before taking part in the experiment. The study was approved by ASST Santi Paolo e Carlo ethics committee. An aqueous solution containing 80 IU/mL of OXT was prepared and dosed in a proper device to obtain an intranasal administration of [4] IU per each puff. The participants were instructed to self-administer the spray (24 IU), 3 sprays per nostril, each containing 4 IU. We decided to use the 24 IU dose of OXT, because this is the most used dose in studies assessing the effects of single-dose OXT on autistic behaviors.[4] We tested the patients before (T0) and 30 minutes after (T1) the OXT administration. The patients have been tested in 2 settings: individually, through the administration of the Reading the Mind in the Eyes Test [5] and through a visual analog scale assessing the level of anxiety, and in a group setting (Supplemental Digital Content, Supplementary Fig. 1, <http://links.lww.com/JCP/A704>). In the group setting, the participants were asked to discuss dilemmas taken from the Moral Judgment Task (MJT).[6] Each dilemma posed a question about a hypothetical action related to the scenario (“Would you...in order to...?”), and they were divided into the following: 10 personal moral dilemmas, 8 impersonal moral dilemmas, and 10 nonmoral dilemmas. In line with the utilitarian theory, utilitarian and nonutilitarian responses were distinguished.[6] At the beginning of each session, the participants were instructed to cooperate to find a common answer to each single dilemma presented; afterward, they received a block of 14 judgments for each session (containing 5 personal moral dilemmas, 4 impersonal moral dilemmas, 5 nonmoral dilemmas), printed on a sheet of paper: they were instructed to read and solve them one by one, and not to proceed to the following one unless they gave a common answer to the one presented. During the 2 sessions, the patients' group psychotherapist was present and was instructed to complete 3 subscales (Communication, Social Interaction, and Creativity) of the Autism Diagnostic Observation Schedule (ADOS) module 4.[7] The ADOS 2 is a reliable semistructured diagnostic tool, based on interviewer's clinical observation. It is designed to create a series of naturalistic settings aimed to elicit social responses, scored by the interviewer according to a specific algorithm. Module 4 was implemented in this study because it is validated for adults and adolescents with fluent language. Data were analyzed with the software SPSS 25.

We recruited 5 patients (1 female) with HF-ASD. The mean \pm SD age was 45 ± 13 years, and the mean \pm SD intelligence quotient was 129 ± 12 . Table 1 showed values at T0 and T1 of each variable assessed.

TABLE 1. Values at T0 and T1 for Each Variable Assessed

| | T0, Mean (SD) | T1, Mean (SD) |
|------------------------------|---------------|---------------|
| VAS—anxiety | 2.4 (2.1) | 0.7 (0.5) |
| RMET—accuracy | 23.1 (2.9) | 24.2 (1.6) |
| RMET—reaction time, s | 392.2 (51.3) | 350.4 (52.6) |
| MJT—moral personal dilemma | 0.2 (0.5) | 0.4 (0.5) |
| MJT—moral impersonal dilemma | 0.5 (0.6) | 0.7 (0.5) |
| MJT—nonmoral dilemma | 0.2 (0.4) | 1.0 (0) |
| Communication | 3.0 (2.7) | 1.5 (1.1) |
| Social interaction | 6.4 (3.8) | 2.9 (2.3) |
| Creativity | 1.6 (1.1) | 0.8 (0.8) |

MJT indicates Moral Judgment Task; RMET, Reading the Mind in the Eyes Test; VAS, visual analog scale

Supplemental Figure 1. Flowchart of the study design. Abbreviations: RTME = “Reading the mind in the eyes” test; VAS = Visual Analogic Scale; MJT = Moral Judgement Task; OXT = oxytocin.



DISCUSSION

In this study, although we decided not to perform any statistical analysis because of the small sample size and the absence of placebo controls, we observed that, after the administration of intranasal OXT, patients with HF-ASD gave more utilitarian responses to nonmoral dilemmas at the MJT and improved their performance in social interaction as assessed by the specific ADOS subscale. These observations, taken together, might lead us to speculate that a single intranasal administration of OXT might have a positive effect on specific social functions in patients with HF-ASD assessed in a group setting. These qualitative observations are in line with previous studies, which underlined the effect of intranasal administration of OXT in improving several social functions such as emotion recognition, social affiliation, and social attention in patients with HF-ASD, assessed in laboratoristic individual settings and evaluated with specific instruments such as the repetitive behavioral scale, the evaluation of comprehension of affective speech, and the evaluation of attention to faces. [8,9] Up to date, only 2 studies have assessed the effects of OXT in patients with ASD not in individual laboratoristic contexts but in technologically made-up social conditions, such as the Social Ball Tossing Game [2] and a more naturalistic setting. [9] Andari et al [2] showed OXT to improve patients' tendency to interact with the partners who showed high levels of cooperation and increased levels of trust for these partners compared with placebo. In the study by Auyeung et al, [10] while freely viewing pictures of faces, patients showed a stronger visual preference for the eye region after OXT treatment compared with placebo. Although Andari et al [2] and Auyeung et al [10] tried to extend results underlying the therapeutic effect of OXT from an individual constrained laboratory setting to a more naturalistic real world social context, they still used a simulated setting. Here, for the first time, a completely real group setting was used. In this study, we also observed, although from a qualitative perspective, that OXT might improve the ability to give more utilitarian responses to nonmoral dilemmas at the Moral Judgment Task in patients with HF-ASD. Moral judgment traditionally depends both on cognitive and emotional processes, relying on the dorsolateral prefrontal cortex and on the ventromedial prefrontal cortex and limbic regions respectively. However, according to Greene's dual process theory, [11] depending on the context (ie, individual features and environmental conditions), one of the two processes might dominate over the other one. Specifically, if the dilemma is moral and personal, and, therefore, the person experiences a strong sense of agency toward the harmful action to be performed, the emotional response unleashed is so strong that it might overcome the cognitive reasoning, and therefore, a nonutilitarian response is given. Recent studies have

highlighted how OXT might have a role in the way of approaching moral dilemmas in neurotypical populations.[12,13] With respect to ASD population, the MJT has been previously used with the aim to assess theory of mind abilities. For example, through a sophisticated task requiring participants to give a moral judgment about an action basing it on the analysis of a person's intentions, Moran et al[14] showed that adults with ASD had difficulties in relying on intentions to judge a situation of accidental harm: conversely and differently from the neurotypical population, they did not judge it differently from the situation of voluntary harm. This finding revealed a Theory of Mind deficit in ASD that influenced explicit moral judgment. A main difference with our study is that, in Moran et al's [14] task, a judgment on other people was demanded, whereas, in our task, perspective taking was required to give a first-person self-referential plan for action. We acknowledge the limitations of our study: first, we conducted the experiment on a single and very small group of patients. Second, the psychotherapist was not blind toward the aim of the study; however, the presence of the therapist's rating might be a strength of the study. Third, the absence of a control group with placebo administration makes it difficult to know to what extent the improvement observed in our sample represented a specific response to treatment intervention. Fourth, looking at the impact on utilitarian versus nonutilitarian responses does not directly impact on social abilities; however, we used the MJT to observe how patients cooperate with each other, evaluating the ADOS subscales Communication, Social Interaction, and Creativity. Finally, at T0, the participants were both OXT and MJT naive, whereas, at T1, the participants were administered OXT and readministered the MJT, albeit different scenarios were used. Therefore, it is impossible to say whether the differences between answers given to the nonmoral dilemmas and the clinician-rated social interaction scale at T0 and T1 are only due to the administration of OXT or might be due also to the repetition of the study tasks.

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