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Oxytocin Selectively Improves Empathic Accuracy: A Replication in Men and Novel Insights in Women

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ABSTRACT

BACKGROUND: Previously, oxytocin, a neuropeptide implicated in human social cognition and behavior, was shown to improve people's ability to dynamically track another's emotional state ("empathic accuracy") specifically for less socially proficient individuals—i.e., healthy adults who score higher on the Autism Spectrum Quotient (AQ); conversely, oxytocin had no effect on empathic accuracy for more socially proficient individuals, who performed well following oxytocin and placebo. Here, we aimed to replicate this finding and investigate the effects of oxytocin on empathic accuracy in women. To date, women have been seriously underrepresented in human oxytocin research, and it is not known whether the effects observed in male-only samples apply to women.

METHODS: In this randomized, double-blind, placebo-controlled, crossover trial, we administered 24 IU intranasal oxytocin (and, on a separate occasion, a matching placebo) to 31 men and 40 women and then measured empathic accuracy. AQ was assessed at baseline (prior to drug administration).

RESULTS: Replicating a 2010 study by Bartz *et al.*, oxytocin selectively improved empathic accuracy for men who scored higher on the AQ, whereas oxytocin did not benefit their lower AQ counterparts. Conversely, we found no effect of oxytocin on empathic accuracy for women (regardless of their AQ score).

CONCLUSIONS: In addition to speaking to reliability, this research is important given interest in using oxytocin to augment social functioning in some psychiatric disorders marked by social cognitive impairments. More generally, this research adds to our understanding of the biological systems that support human sociality and provides further evidence for the role of oxytocin therein.

Keywords: Autism spectrum quotient, Empathic accuracy, Human, Intranasal, Oxytocin, Replication

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Difficulties understanding the mental and emotional states of others is a central feature of many psychiatric disorders including autism spectrum disorder (1,2), schizophrenia (3), and schizotypal personality disorder (4). This ability is critical to successful social functioning because it helps individuals to navigate their social world. It allows them to explain the actions of others and to predict their future actions (1), and it is a crucial building block for more complex interpersonal processes such as empathy that define human social relationships. Although considerable work has revealed the neural correlates of emotion recognition, and empathy more broadly [see, e.g., (5)], less is known about the neurochemical systems involved. Identifying the biological underpinnings of basic dimensions of human functioning is critical to advancing our understanding not only of the potential causes of mental disorders (or, more precisely, key symptoms of those disorders), but also of potential treatments (6).

One widely recognized candidate in this regard is the neuropeptide oxytocin: over 4 decades of research indicate that oxytocin plays a role in regulating social behavior and aspects of social cognition in nonhuman animals (7–9). Recent research suggests that oxytocin is also involved in human social cognition. For example, research using intranasal technology to experimentally manipulate the availability of oxytocin in humans has shown that oxytocin facilitates mental state attribution accuracy, or "mindreading" [e.g., (10)]. Close inspection of the literature, however, indicates that effects of oxytocin on emotion processing have not replicated well (11). Although such variability may signal a weak or nonexistent effect, much of this work has not taken into account person characteristics, which can often moderate the social effects of oxytocin (12,13). In one of the first demonstrations of oxytocin's person-dependent effects, Bartz *et al.* (14) administered intranasal oxytocin or placebo and had participants perform a naturalistic empathic accuracy task (15) in which they watched videos of targets discussing emotional autobiographical events and rated, continuously, how they thought the target was feeling. To index empathic accuracy, these continuous ratings were compared with the targets' own continuous ratings of how they were feeling. In this way, the task is designed to capture the kinds of social cognitive abilities required to decode social information as it unfolds in everyday life, which is dynamic and fleeting and involves the integration of multiple sensory modalities. Results showed no main effect of oxytocin on empathic accuracy; rather, oxytocin's effect was moderated by individual differences in social proficiency, assessed by the Autism Spectrum Quotient (AQ) (16). Consistent with prior work (17), in the placebo condition, the more participants endorsed traits of autism, the poorer they performed on the empathic accuracy task. Critically, however, oxytocin selectively improved empathic accuracy for high AQ participants such that, following oxytocin, their performance was indistinguishable from their low AQ counterparts. These findings add to the literature supporting the functional role of oxytocin in human social cognition; moreover, by showing that oxytocin was selectively helpful in facilitating empathic accuracy for less socially proficient individuals, but that it had negligible effects for more socially proficient individuals, these findings support the notion that variation in social proficiency may be related to the oxytocin system.

The observation that oxytocin selectively improves social cognition and/or emotion recognition for less socially proficient individuals has been conceptually replicated. Radke and de Bruijn (18) found that individual differences in trait empathic concern moderates the effects of oxytocin on the Reading the Mind in the Eyes Task (RMET) (17), with oxytocin selectively benefiting individuals low in empathic concern. Similarly, Feeser *et al.* (19) found that oxytocin selectively facilitates RMET performance for individuals low in trait empathy, and Luminet *et al.* (20) found that oxytocin selectively facilitates RMET performance for individuals high in alexithymia (i.e., the inability to describe one's own emotional experience). Finally, Leknes *et al.* (21) found selectively beneficial effects of oxytocin for individuals scoring lower on an emotional sensitivity task.

Although these conceptual replications speak to generalizability, direct replication is critical to address questions about the reliability of an effect—an issue that has become a concern in psychology, psychiatry, and other sciences (22–24), and for human oxytocin research (25,26). Direct replication is particularly important in this case given interest in using oxytocin therapeutically in psychiatric disorders marked by impaired social cognition, including clinical trials in schizophrenia [e.g., (27–29)] and a multisite, multimillion dollar clinical trial in autism spectrum disorder (SOARS-B [Study of Oxytocin in Autism to Improve Reciprocal Social Behaviors]; https://clinicaltrials.gov/ct2/show/NCT01944046). Most prior studies investigating the effects of oxytocin on mental state attribution accuracy used the RMET, which requires participants to attribute mental states from photos of the eye region. Although widely used, the RMET may not fully capture the kind of complex social cognition required to navigate everyday social interactions, which, as noted, is dynamic, fleeting, and multimodal. Indeed, interventions that improve performance on more simplistic social cognition tasks, like the RMET, do not always translate to improvements in social functioning (30,31).

Another major limitation of the work on oxytocin and social cognition is that findings are based largely on men. Until recently, the vast majority of intranasal oxytocin studies have involved male-only samples. Importantly, studies in nonhuman animals have observed sex differences in oxytocin functioning, and some studies suggest that the effects of oxytocin in humans can be sexually dimorphic [for reviews, see (32–34)]; given this, it is critical that researchers verify whether effects observed in men extend to women.

Thus, the first aim of the present investigation was to replicate the finding that individual differences in social proficiency (measured by the AQ) moderate the effects of oxytocin on empathic accuracy in men. The second aim of this research was to investigate the effect of oxytocin on empathic accuracy in women. Following Bartz *et al.* (14), we administered 24 IU intranasal oxytocin and placebo (within subject) and then had participants perform the aforementioned empathic accuracy task; individual differences in social proficiency were assessed at baseline with the AQ. In line with Bartz *et al.* (14), we hypothesized that oxytocin (vs. placebo) would selectively facilitate empathic accuracy performance for men who are less attuned to social information (high AQ scorers), but it would have negligible effects for their more socially proficient counterparts. Regarding women, we had no specific predictions about the effects of oxytocin on empathic accuracy because, as noted, oxytocin's effects can be sexually dimorphic.

METHODS AND MATERIALS

Participants

Healthy male and female adult participants were recruited from the McGill University community. Participants were required to be between the ages of 18 and 40 years, and in good physical health. Exclusion criteria included 1) use of drugs known to interact with Syntocinon (synthetic oxytocin; Novartis, Cambridge, MA), 2) intake of medication, including over-the-counter medications, and recreational drugs 24 hours before testing (with the exception of oral contraceptives[1]), 3) known allergy to Syntocinon, or to preservatives contained in the nasal spray, 4) nasal disease or obstruction, 5) smoking $>$ 15 cigarettes/day, 6) diagnosis of psychiatric disorder(s), and/or 7) medical condition that could interfere with conduct of the study. Women who screened positive for pregnancy, or who refused to take birth control during the study period, were also excluded.

Eighty participants were enrolled and underwent a medical screening to confirm eligibility; 78 met our eligibility criteria and 73 completed both testing sessions. One participant did not have empathic accuracy data (due to technical error) and 1 participant did not disclose a gender so could not be included in the analyses. Thus, the final sample consisted of 31 men (mean age: 22.7 $\pm$ 3.49) and 40 women (mean age: 21.6 $\pm$ 2.70). Men and women did not differ in age ($t_{69} = -1.58$; $p = .12$) or ethnicity ($\chi^2_6 = 5.35$; $p = .50$). All participants gave written informed consent and were given \$40 to \$50 for day 1 (compensation varied according to medical screening time) and \$30 for day 2. The study was approved by the McGill University Faculty of Medicine Institutional Review Board.

Of note, this kind of research is resource intensive and costly, which makes it difficult to obtain large samples. However, our use of a within-subject design affords us

[1] Eight women reported using oral contraceptives; the analyses reported below do not differ if these women are excluded from the analyses.

considerably more statistical power than the more typical between-subjects design used in oxytocin studies because one is able to minimize error variance related to individual differences; a within-subjects design is also optimal for assessing person-moderated effects because individual differences are matched between drug conditions. That said, we appreciate that smaller samples are vulnerable to spurious effects; to address this, we also pooled the data from this study with that from the original study by Bartz *et al.* (14) to obtain a larger sample size.

Design and Procedures

Following Bartz *et al.* (14), we used a randomized, double-blind, placebo-controlled challenge procedure, in which participants received a single 24-IU dose of intranasal oxytocin (Syntocinon) or a matching placebo (i.e., containing all ingredients except the active substance) on two occasions, approximately 1 to 3 weeks apart. Drug and placebo were imported from Victoria Apotheke Zürich (Zurich, Switzerland); administration order of drug or placebo was counterbalanced across participants.

Potential participants first underwent a medical screening (and urine pregnancy test for women) to determine eligibility. Participants meeting eligibility criteria completed a series of self-report questionnaires (see the Supplement for details), including the AQ, and then self-administered 24 IU intranasal oxytocin or placebo under the supervision of a trained experimenter. Approximately 45 minutes later, participants completed a mood index and two short tasks unrelated to the present investigation [the graphesthesia task (35) and the Rubber Hand Illusion (36)] and then began the empathic accuracy task (approximately 65 minutes after drug administration). After the empathic accuracy task, which lasted approximately 25 minutes, participants completed additional unrelated tasks and questionnaires. Participants returned 1 to 3 weeks later and received the alternate compound and completed the empathic accuracy task again, with different stimulus videos to avoid practice effects.

Autism Spectrum Quotient. The AQ is a 50-item self-report measure assessing traits associated with autism in adults of normal intelligence—specifically, social and communication skills, attention to detail, tolerance of change, and imagination (16). Possible AQ scores range from 0 to 50 (higher scores reflect more autistic traits). In this study, AQ scores ranged from 5 to 33 (mean: 17.64 $\pm$ 5.09). In contrast to previous research (16), we did not find a significant difference in AQ scores between men (mean: 17.01 $\pm$ 5.2) and women (mean: 18.13 $\pm$ 4.9), $F_{1,69} = 0.835$, $p = .364$. We suspect that this may be because our female participants were more likely to be in the Faculty of Science, and prior research indicates that there tend to be no gender differences in AQ within the category of science students [(16); indeed, our means are very similar to the mean for the science majors from that report, which was 18.5 $\pm$ 6.8].

Empathic Accuracy Task. In this task, participants watch a series of short videos of male and female targets discussing positive and negative autobiographical events (while facing the camera); participants use key-presses to provide continuous ratings, on a 9-point Likert scale, of how positive or negative the target is feeling during the narrative (15). Importantly, the targets themselves also watched their own videos and made similar ratings of how positive or negative they felt while discussing these events. Empathic accuracy is operationalized as the correlation between affect ratings made by perceivers and targets. Specifically, we averaged each participant's affect ratings across 2-second periods, and each 2-second mean served as a point in a time-series analysis. We then correlated perceiver affect ratings with target affect ratings, which yielded a separate correlation coefficient reflecting each participant's empathic score for each video clip. In total, there were 566 accuracy scores: 71 participants $\times$ four clips per participant $\times$ 2 testing days (two video clip accuracy scores were excluded because the participants did not generate enough responses to calculate a score).

Statistical Analyses

To test whether we replicated our previous observation that oxytocin selectively improves empathic accuracy in men who score higher (vs. lower) on the AQ, we followed Bartz *et al.* (14) and conducted a multilevel model analysis (MLM) (37) in which empathic accuracy video was nested within participant. Specifically, empathic accuracy scores were entered as the dependent variable, with drug (0 = placebo; 1 = oxytocin), AQ scores (*Z*-standardized), and their interaction terms as fixed effects, and subject ID and video number as random effects. [*Note:* In the previous study (14), target expressivity was included as a covariate; however, we did not have target expressivity in the present investigation, so we included video number as a random effect to control for idiosyncratic video content.] As noted, we also pooled the data for men from the current study with that from the original study (14) to bolster our sample size of male participants, and we conducted parallel analyses on this larger sample; in this way, we could investigate the possibility of spurious effects and test whether the key interaction effect differs between the two studies.

To investigate the effects of oxytocin on empathic accuracy in women, we ran parallel analyses on the full sample (i.e., men and women from the current study) to maximize power, and we included gender (0 = women; 1 = men), drug (0 = placebo; 1 = oxytocin), and AQ scores (*Z*-standardized), and their three-way interaction, as a fixed factor. Again, subject ID and video number were included as random effects.[2]

For all analyses, confidence intervals were boot-strapped. Simple effects were decomposed using the formulas described by Preacher *et al.* (38)—specifically, testing the slope of empathic accuracy on drug at the mean of AQ and conditional values of 1 SD above and below the mean of AQ. Given that the choice of $\pm$ 1 SD is somewhat arbitrary, we supplemented these analyses with the Johnson-Neyman technique (39,40) to identify the precise range of AQ scores

[2] For both sets of analyses, we also ran separate models including drug administration order as a covariate; as in the original paper (14), we found no drug-order effect ($p > .9$), and including order did not qualify the effects reported below, so we took order out of the model to be consistent with the original study analyses.

Table 1. Effects of Oxytocin (vs. Placebo) and AQ on Empathic Accuracy in Replication Sample and Pooled Samples (Men Only)

	Replication Sample (n = 31, Within Subject)			Pooled Sample (n = 58, Within Subject)		
Effect	b	t	p	b	t	p
Drug × AQ	0.090	3.038	.0027	0.095	3.308	.0010
Simple Effect for Men	b	Z	p	b	Z	p
AQ-PLC Condition	−0.042	−1.686	.0918	−0.070	−3.144	.002
Drug (+1 SD AQ)	0.096	2.134	.0328	0.123	2.908	.004
Drug (−1 SD AQ)	−0.084	−2.088	.0368	−0.068	−1.696	.090

Johnson-Neyman range of significance is −0.903 to 0.840 for replication sample and −1.193 to 0.364 for pooled sample. Slopes are significant outside this region.

AQ, Autism Spectrum Quotient; PLC, placebo.

within which the simple slope of empathic accuracy on drug is significantly different from 0.

All statistical analyses were conducted using R (41) and the lme4-package for MLM (42). We did not analyze the data from this investigation before stopping the study, and we preregistered our data analysis plan at OSF (https://osf.io/c2qbf/) prior to conducting any analyses.

RESULTS

Effects of Oxytocin on Empathic Accuracy in Men

The results of the MLM explaining empathic accuracy scores, with drug and AQ scores, revealed a significant drug × AQ interaction, b = 0.09 (SE = 0.03; 95% confidence interval: 0.03–0.15), $t_{200.16}$ = 3.04, $p < .01$.[3] As indicated in Table 1 (left column), and consistent with the previous investigation, simple effect analyses revealed a significant difference between oxytocin and placebo for male participants scoring higher (+1 SD) on the AQ, b = 0.10, Z = 2.13, p = .03; unexpectedly, low AQ participants showed the opposite pattern, performing worse following oxytocin (vs. placebo), b = −0.08, Z = −2.09, p = .04. Also, as indicated in Table 1 (right column), analyses of the pooled data (n = 58; within subject) indicate that the drug × AQ interaction effect held—indeed, it becomes slightly stronger in this larger sample. Again, the simple effect analyses showed a significant difference between oxytocin and placebo for male participants scoring higher (+1 SD) on the AQ. Notably, the unexpected effect of drug for low AQ participants did not remain significant in this larger sample, suggesting that this effect may be spurious. Importantly, there was no effect of study (p = .60), indicating that the drug × AQ interaction effect was similar in both samples.

Effects of Oxytocin on Empathic Accuracy in Women

Turning to the analysis that included women, MLM results revealed a significant three-way interaction: drug × gender × AQ, b = 0.11 (SE = 0.04; 95% confidence interval: 0.03–0.20), $t_{477.85}$ = 2.63, $p < .01$ (see Figure 1).[4] As in the analyses with men, simple effect analyses revealed a significant difference between oxytocin and placebo for male participants scoring higher on the AQ, b = 0.09, Z = 1.99, p = .046, whereas low AQ participants showed the opposite pattern, b = −0.09, Z = −2.10, p = .035. For women, however, simple effect analyses showed no effect of drug, AQ, or the drug × AQ interaction predicting empathic accuracy. There was no significant difference between oxytocin and placebo for female participants scoring higher (+1 SD) on the AQ, b = −0.06, Z = 1.52, p = .129, nor was there a significant difference between oxytocin and placebo for women scoring lower (−1 SD) on the AQ, b = −0.02, Z = −0.40, $p > .25$. No other simple effects reached conventional levels of statistical significance (all other $Z < 1.95$). A complete description of the MLM results for women can be found in the Supplemental Table S2.

DISCUSSION

The aim of this research was twofold: first, to replicate the observation that oxytocin selectively facilitates perceiver-target accuracy of real-time social-emotional inferences for men who are less socially proficient at baseline; second, to investigate the effect of oxytocin on empathic accuracy in women, a population that is underrepresented in intranasal oxytocin research and in psychiatry research in general (43).

Regarding our first aim, as predicted, and replicating Bartz *et al.* (14), we found that individual differences in AQ—our operationalization of social proficiency—moderated the effects of oxytocin on empathic accuracy, with oxytocin selectively improving empathic accuracy performance for less socially proficient men. Concerns have been raised about the reproducibility of findings in psychology and psychiatry [e.g.,

[3] Recent advances in MLM advocate the use of "maximal models" that include a maximal random effects structure to control for type I errors [e.g., (56,57)]. To this end, we ran another model in which we included a random slope for our within-subject factor (drug) for both the target video and subject ID [cf. (56)]. Critically, using this more conservative model, the drug × AQ interaction in men remains significant, b = 0.09, $t_{27.07}$ = 2.65, p = .013, and the simple effect is significant at 1.2416 SD. For a complete summary of the results from these analyses, interested readers are referred to Supplemental Table S1.

[4] As with the two-way interaction, the triple (gender × drug × AQ) interaction remains significant (b = 0.11, p = .027) using the model that includes a maximal error variance.

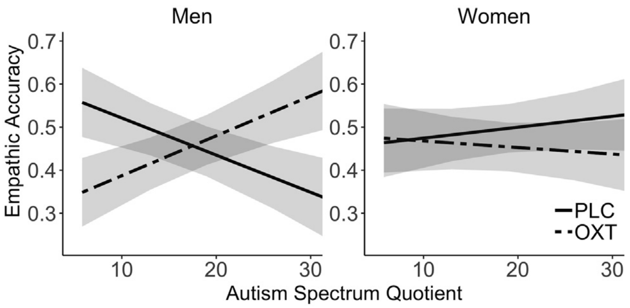

Figure 1. Results of the multilevel model analysis predicting empathic accuracy as a function of gender and Autism Spectrum Quotient raw score for the oxytocin (OXT) condition (dashed line) and placebo (PLC) condition (solid line). The shaded areas reflect the standard error of the mean. Higher numbers on the Autism Spectrum Quotient reflect poorer social cognitive proficiency. Higher numbers on the empathic accuracy index reflect superior performance. Predictive values are shown only for observed levels of the Autism Spectrum Quotient.

(22,24)] and, specifically, in human oxytocin research (26). For example, Walum *et al.* (26) argued that many of the reported effects in the intranasal oxytocin literature may not be true effects because they are based on small samples. One challenge with this research is that it is costly and resource intensive, which makes obtaining large samples difficult. Independent replication is one way to address concerns about the reliability of an effect. Moreover, our pooled analysis speaks to spurious effects that can arise in smaller samples. We believe that these findings add to our understanding of the biological systems that support human social cognition and provide further evidence for the role of oxytocin therein. In line with current thinking (6), variability in social proficiency may reflect a basic dimension of human behavior. That oxytocin was selectively helpful in facilitating empathic accuracy for less socially proficient individuals, but had negligible effects for more socially proficient individuals, suggests that oxytocin plays a functional role in human social cognition and that variation in social proficiency may be related to the oxytocin system.

Of note, in the original study (14), there was no effect of oxytocin on empathic accuracy for more socially proficient men, who performed well following placebo and oxytocin. In the present investigation, however, more socially proficient men performed slightly worse following oxytocin. Interestingly, Human *et al.* (44) observed a similar phenomenon: oxytocin was selectively helpful in augmenting prosocial tendencies in less extraverted participants, whereas oxytocin did not augment prosocial tendencies in more extraverted participants (who were already prosocial)—in fact, highly extraverted participants showed a slight decrease in prosocial tendencies following oxytocin. As Human *et al.* (44) noted, there may be an optimal level of social engagement, and moving people beyond this point could have negative interpersonal consequences. Similarly, there may be an optimal level of social sensitivity that facilitates empathic accuracy, but increasing social sensitivity beyond this point may undermine accuracy [also see (45)]. High levels of social sensitivity could heighten perceptions of emotion intensity, which could undermine accuracy, especially if the intensity effect is specific to some emotions but not others [e.g., (46,47)]. Alternatively, high levels of social sensitivity could make participants more personally distressed about the target's plight and, consequently, undermine accuracy. Indeed, the divergent findings for low- and high-AQ participants could explain why the simple main effect of oxytocin on emotion processing has not replicated well. That said, the drug effect for low AQ participants did not hold in the pooled dataset, so this interpretation is speculative. Future work is needed to probe the effects of oxytocin in more socially attuned individuals.

Regarding our second aim, we found no effect of oxytocin on empathic accuracy for women, regardless of their AQ score. The main finding from this line of work is that oxytocin is especially helpful in augmenting social cognition for less socially proficient individuals. The lack of an effect for women thus could be because they were more socially proficient than men. However, we found no gender differences in AQ [possibly because, as noted, our female participants were more likely to be science majors, and prior work indicates that within the category of science students, there are often no gender differences in AQ (16)]. Moreover, we found no gender difference on the empathic accuracy task in the placebo condition. Thus, at least in this sample, our female participants did not appear to be more socially proficient than the male participants.

In our view, a more likely explanation for the lack of an effect for women may have to do with the differential effects of oxytocin in women. As noted, sex differences in oxytocin functioning have been found in nonhuman animal studies, and some studies suggest that the effects of oxytocin in humans can be sexually dimorphic [for reviews, see (32–34)]. For example, oxytocin administration typically attenuates amygdala reactivity in men [e.g., (48,49)] but either has no effect (50) or can increase amygdala activity in women (51,52). Given the role of the amygdala in emotion processing [e.g., (53)], it is possible that the gender differences in oxytocin's effect on emotion processing could be due to oxytocin's differential effects on the amygdala (or neural activity and coupling more generally) in men and women. Alternatively, some have argued that other hormones may alter the effects of oxytocin in women (54); however, we did not find that women showed more variance in empathic accuracy task performance than men in the oxytocin condition (see the Supplement). The differential effects for men and women could also be driven by different dose-response relationships between men and women (55). Finally, the null effects for women could be a type II error. Future work is needed to better understand the pattern and underlying cause for gender differences in response to oxytocin.

In closing, we replicate the observation that oxytocin selectively improves performance on a naturalistic empathic accuracy task for men who are less socially proficient or sensitive. By contrast, oxytocin had no beneficial effects for men who are more socially proficient, nor did oxytocin have beneficial effects on empathic accuracy performance for women (regardless of their social proficiency level). In addition to providing evidence that speaks to concerns about reproducibility, we believe that these findings are important given recent interest in the therapeutic potential of intranasal oxytocin for improving social cognition in disorders marked by impaired social functioning. Our sample consisted of healthy individuals; therefore, caution is warranted when making inferences based on these findings about the effects of oxytocin in clinical samples. That said, variability in social proficiency may reflect a basic dimension of human behavior that lies on a continuum from less to more extreme; in this way, we hope our findings can be used to guide predictions about when, and for whom, oxytocin could be expected to improve social cognition.

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The study concept and design was developed by JAB and SAK. JPN, SAK, and JAB performed the data analyses and interpretation. JAB and JPN drafted the manuscript, and SAK and P-PT provided critical revisions. P-PT oversaw all medical aspects of the study, including advising on inclusion and exclusion criteria, medical evaluation procedures, and adverse events. All authors approved the final version of the paper for submission.

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ARTICLE INFORMATION

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