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The Role of Intranasal Oxytocin on Social Cognition: An Integrative Human Lifespan Approach

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Abstract

Purpose of Review: This narrative review synthesizes research from the last two decades on the modulatory role of intranasal OT administration (IN-OT) on social cognition in early life, young/middle adulthood, and older adulthood. Advances and knowledge gaps are identified, and future research directions are discussed within an integrative human lifespan framework to guide novel research on IN-OT and social cognition.

Recent Findings: Current evidence regarding IN-OT modulation of social-cognitive processes, behavior, and related neurocircuitry is mixed, with some studies suggesting benefits (e.g., improved social perception/interactions, emotion processing) depending on contextual (e.g., social stimuli) and interindividual factors (e.g., age, sex, clinical status). Current research, however, is limited by a focus on isolated life phases, males, and select clinical populations as well as a lack of standardized protocols.

Summary: This literature-based reflection proposes that greater generalizability of findings and scientific advancement on social-cognitive modulation via IN-OT require standardized, multi-method, longitudinal, and cross-sequential assessments in well-powered, well-controlled, and representative samples in line with an integrative lifespan approach, which considers development as a lifelong dynamic process involving both change and stability characterized by the interplay between genetic, neurobiological, and socio-behavioral factors.

Keywords

Oxytocin; Intranasal Administration; Neuropeptide; Hormone; Lifespan Development; Social Cognition

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1. Introduction

Oxytocin (OT) is a nine-amino-acid neuropeptide that is mainly synthesized in the hypothalamus and serves various evolutionarily conserved physiological, behavioral, and cognitive functions vital for survival in both humans and animals (e.g., metabolic and cardiovascular regulation, parental and other adaptive social behaviors) [1,2]. Though not exclusively a "social" neuropeptide, in recent years, OT has garnered particular interest as a modulator of human social cognition [2,3]. In early life as well as in adulthood, unimpaired social-cognitive abilities (e.g., social perception, processing, and related decision-making) are critical for accurate interpretation of social cues and facilitation of social interactions. The need for preserved, adaptive social cognition may also be particularly relevant in advanced age when declines are more evident across functional domains, such as in source memory [4], emotion identification [5], and deception detection [6]. Though the literature has attributed age-related social-cognitive declines to motivational and brain changes, the role of the OT system, and related neurocircuitry, in these declines is not well understood yet [7,8].

Intranasal OT (IN-OT) is currently the most practical, commonly used, and non-invasive route of exogenous OT delivery to the human brain [9,10]. IN-OT can be self-administered via a hand-held spray (most common) or through other specialized methods (e.g., breath-powered devices, nebulizers) [9,11] and has been increasingly utilized to investigate the modulation of social cognition in healthy and clinical populations [12]. IN-OT can impact social and emotional cue processing (e.g., facial emotion identification [13], social reward [14]) and has demonstrated potential to counter social-cognitive dysfunction in different phases of the lifespan (e.g., early development [15], adulthood [16], and aging [17]). Plasma OT concentrations have shown to peak at 15 minutes after IN-OT administration and decline after 75 minutes [18]. Whereas, peak OT response corresponding to regional cerebral blood flow has been reported to be between 39 and 51 minutes after intranasal administration in healthy men [19]. Alteration of regional cerebral blood flow by IN-OT has also been observed for up to two hours after administration [20]. Longer-term IN-OT effects would likely depend on repeated administration in therapeutic contexts [9,12].

It is suspected that IN-OT exerts its modulatory effects through different mechanisms, such as by increasing central OT concentrations via nose-to-brain pathways (e.g., olfactory and trigeminal nerves) [10] and/or altering cerebral blood flow (e.g., in the amygdala) [20]. As researchers continue to investigate IN-OT's therapeutic potential, more research is needed regarding its pharmacokinetic mechanisms of action towards the development of more precise methods for non-invasive delivery to the brain.

Consistency in the efficacy of IN-OT in modulating social-cognitive processes and behaviors [21] and ameliorating social-cognitive dysfunction [22] also needs to be demonstrated, including across development, before broader therapeutic use is possible. Currently, the replicability of IN-OT effects on specific social-cognitive processes and behaviors (e.g., emotion processing [23]; trust [24]) remains in question. To this end, there is an urgent need for more direct, rather than conceptual, replication studies [25]. Also, the majority of IN-OT

studies on human social cognition, to date, is limited by a focus on distinct/isolated age groups without an attempt to integrate findings across the human lifespan.

Development is a lifelong dynamic process involving both change and stability characterized by the interplay between genetic, neurobiological, and socio-behavioral factors. Integrating IN-OT effects on social cognition across the lifespan has the potential to broaden and generalize understanding of OT mechanisms and modulation across different social contexts, individuals, and developmental phases. OT response is not uniform across individuals [9], but rather varies by social situations (e.g., social/emotional memory, perception, recognition, sharing; Bartz et al., 2011) and interindividual factors (e.g., sex and age; [27–29]. We propose that an integrative lifespan approach to IN-OT research offers a more comprehensive understanding of OT mechanisms and modulation of social cognition, which can inform the design of efficacious treatment plans across developmental phases [9,30].

Towards such an integrative perspective, in this narrative review, we synthesize evidence accumulated over the last two decades from studies on IN-OT and social cognition in early life, young/middle adulthood, and older adulthood (see Table 1 for an overview of studies). Advances and current limitations of these still largely parallel lines of research are discussed and developed into constructive suggestions for future investigation within the proposed integrative lifespan framework (see Fig. 1).

2. IN-OT Research on Social Cognition in Early Life, Young/Middle Adulthood, and Older Adulthood

Most investigative work on IN-OT modulation of social cognition has been reported in isolated lines of work on early life, young/middle adulthood, and older adulthood without integration across the human lifespan. Evidence from these distinct investigative fields is briefly summarized and reflected on next.

2.1. Early Life

OT is involved in critical functions that support early life including uterine contractions, lactation, and parental behavior [31]. The endogenous OT system is highly plastic during early development [32]. In humans, OT gene expression occurs within 15 weeks of gestation. By 25–26 weeks, the supraoptic and paraventricular nuclei of the hypothalamus have fully developed, with OT neurons comparable to adults [33]. Birth is especially critical for the release of mature OT and thus the propagation of the endogenous OT system. Also, there is an elevated level of OT receptor (*OXTR*) expression at birth, which undergoes up- and down-regulation throughout development [1].

The expansion of socioemotional and cognitive abilities (e.g., bonding, emotion identification, perspective-taking) is evident across early development. However, certain factors that impact the OT system (e.g., brain/behavioral disorders, early life adversity) may disrupt these abilities [34,35]. For example, developmental defects of the hypothalamus and related deficiencies in OT signaling can contribute to communication and bonding difficulties [1,36].

The majority of IN-OT research on social and emotional function in early development has been conducted in individuals with neurodevelopmental disorders [32], including Prader-Willi Syndrome (PWS; though often as outcomes secondary to feeding impairments) [15,37,38]. PWS is a genetic disorder that severely impairs feeding behaviors and the ability to appropriately interpret social information and interact with others [39]. Individuals with PWS have reduced paraventricular nuclei volume and OT-expressing neurons [40,41].[1] IN-OT research on PWS has frequently leveraged third-party observation (e.g., parent, clinician) to assess social behavior and is limited to assessments of social and emotional information processing in youth.

Current evidence supports some benefits from IN-OT on social behaviors in PWS during early development (but see [41] for a discussion of methodological limitations). For example, 7 days of IN-OT on infants with PWS was associated with improved experimenter-blinded scores on infant–parent withdrawal behavior and social interactions (e.g., eye contact, facial expressions, social engagement) [15] and increased functional connectivity of an orbitofrontal network which was correlated with improved social engagement across three dosing schedules.

OT-enhanced social behavior and emotional experience in individuals with PWS, however, appear to vary by age and therapeutic benefits may not be apparent until several weeks of administration [9,12]. For example, IN-OT over 4 weeks was associated with improved parental evaluations of anger and sadness as well as social behavior in children under 11 years but not older [37]. In contrast, 5 days IN-OT did not improve socialization in children aged 11 and younger [38]. Similarly, evidence of IN-OT's efficacy in modulating social behaviors and emotions is mixed in adolescents and younger adults. For example, in adults with PWS, acute (i.e., single-dose) IN-OT resulted in increased trust in others, decreased disruptive behavior, and less sadness as scored by caretaking staff [42]. This study, however, found no OT-related improvement for validated social-cognitive measures such as the Reading the Mind in the Eyes Test (RMET). Similarly, no RMET improvement was reported after 8 weeks of IN-OT in 12 to 30 year-olds [39].

The stabilization of neuronal deficiencies in the endogenous OT system with age may contribute to mixed findings among individuals with PWS who have aged out of early development [39]. Inconsistent findings may also be due to variations in OT dosage, with lower doses potentially reducing the possibility of binding to closely-related vasopressin receptors, yielding more favorable results than higher doses [38]. Additionally, variations in administration frequency and/or outcome measures across studies may underlie mixed findings [9]. In particular, it appears that studies that used behavioral measures of social cognition, like the RMET, did not observe benefits from IN-OT while studies that utilized third-party observation reported improvements.

Currently, it is difficult to draw definitive conclusions as to whether IN-OT has practical utility for the treatment of social-cognitive deficits in PWS. Moving forward, a combination of behavioral experimental tasks with clinical measures of daily social functioning will

[1]For a review on OT and social cognition in PWS see [41].

inform OT's social-cognitive benefits in everyday interactions [41]. Furthermore, future research is needed to determine if early, compared to later, IN-OT intervention is particularly beneficial in PWS. Finally, identification of the neural processes underlying social-cognitive changes resulting from IN-OT across early development will advance mechanistic understanding of OT's role in social cognition in PWS.

Another neurodevelopmental disorder in which IN-OT effects on social cognition have been studied is Autism Spectrum Disorder (ASD) [43–47]. Similar to PWS, individuals with ASD experience difficulties processing social information and communicating with others among other symptoms (e.g., repetitive behavior). Most work has focused on males and those with high-functioning ASD (i.e., no intellectual disability) [48] and, in sum, has pointed to IN-OT related improvement in children and adolescents [49] (e.g., enhanced emotion identification [43]).[2]

Work in this domain has also explored IN-OT effects on the brain during social and emotional information processing. For example, acute IN-OT was associated with greater activation to social stimuli, and attenuated activation for non-social stimuli, in regions of the "social brain" (e.g., striatum, nucleus accumbens, superior temporal sulcus, premotor cortex) [44]. Similarly, acute OT resulted in greater neural activity and connectivity in these brain regions during social perception [50]. Findings indicate that acute IN-OT benefits social cognition in children and adolescents with ASD, possibly via neuromodulation in social brain regions.

Utilizing repeated OT administration, ranging from several weeks to months, has also gained traction in this research arena. For example, several weeks of IN-OT was linked to improved social responsiveness in children with ASD [51,52], especially among those with the lowest levels of pre-treatment endogenous OT [52]. Similarly, in children and adolescents, longer-term IN-OT improved social interaction/communication [45,53] as well as other social-cognitive processes (i.e., face recognition, theory of mind (ToM), empathic accuracy) [54].

Together these findings indicate that acute and repeated IN-OT modulate brain and behavior in youth with ASD (but see [46,47]). Of note, high-functioning males constitute the typical subject profile in these clinical investigations, while not representative of all individuals impacted by this disorder. The inclusion of females and lower-functioning individuals is warranted for a comprehensive evaluation of therapeutic efficacy. In this context, special attention to biomarkers associated with the endogenous OT system (i.e., peripheral OT levels, OT receptor distribution, and *OXTR* polymorphisms) has the potential to enhance our understanding of the role of OT on social cognition in ASD [52].

2.2. Adulthood

Most work on IN-OT modulation of social-cognition has been conducted in younger adults, with some samples extending into middle age. Initially, OT-related enhancement of social-cognitive capacities, including ToM [55] and trust [56], was reported for healthy adult males. In further support of IN-OT's beneficial effects on social-cognitive processes, more recent

[2]For reviews on OT and social cognition in ASD see [49,54].

meta-analytic findings demonstrated positive IN-OT effects on emotion processing [13,23] and trust [57], in healthy men and women. The literature discussed these effects as a potential result from IN-OT enhancing social cue salience [58], perhaps by modulating early attentional resources [59] and possibly without perceptual awareness [60].

Neuroimaging (e.g., fMRI) and electrophysiological (e.g., ERP/EEG) methods have been increasingly used to delineate the neural substrates of OT function in adulthood. The amygdala, midbrain, and striatum were initially proposed as key targets of OT's social-cognitive action [61,62]. A recent meta-analysis extended understanding of brain mechanisms by indicating that acute IN-OT alters functional activity across various brain regions and networks, and most robustly in the left insula, across a variety of social-cognitive tasks in young men and women [63]. Additional meta-analytic evidence supports that IN-OT increased activation of the superior temporal gyrus [64,65] and caudate during social and emotion processing while reducing bilateral amygdala activity, particularly during negative information processing [65].

During adulthood, IN-OT has also received particular attention for use in neurodevelopmental and psychiatric disorders characterized by social-cognitive impairments, including ASD and schizophrenia (SCZ) [49,66]. In this context, IN-OT has emerged as a potential pharmacological treatment for social-cognitive dysfunction, based on endogenous OT's roles in social cognition and behavior and given initial promising findings of IN-OT administration in these clinical populations [54,67]. For example, a recent meta-analysis using data from randomized controlled trials showed a significant, yet small, effect of IN-OT on ToM (while no effect on empathy or emotion recognition was observed) in adult clinical populations, including ASD and SCZ [68].[3]

As noted above, ASD is characterized by impaired social functioning and communication. IN-OT research has shown promise in ameliorating social-cognitive dysfunction for adults with ASD [54]. For example, acute IN-OT increased amygdala activity during face processing [69] and was associated with enhanced ToM and insula activity in men with ASD [70]. IN-OT also improved social reinforcement learning among men with ASD and modulated reward prediction error-related activation of the nucleus accumbens, supporting IN-OT as a candidate for adjunctive treatment to behavioral interventions in social learning [71]. Longer-term (6 weeks) IN-OT, furthermore, resulted in improved ToM, life quality, as well as functional activity in and connectivity of the medial prefrontal cortex (mPFC) [72,73]; it also improved social-cognitive performance and social reciprocity in men with ASD (but see [74] for null effects on social responsiveness from 4-weeks of IN-OT). In sum, both acute and repeated IN-OT studies largely point to beneficial social-cognitive effects in men with ASD.

SCZ and related disorders are characterized by positive (e.g., hallucinations, delusions) and negative (e.g., blunted affect, asociality) symptoms as well as cognitive impairments (e.g., working memory, processing speed), which contribute to deficits across multiple social-cognitive capacities [75]. IN-OT benefits for treating social-cognitive dysfunction in SCZ

[3]For similar findings regarding emotion recognition in clinical populations see [23].

have been demonstrated in social contexts that involve higher-level processing (e.g., recognition of social faux pas), compared to lower-level processing (e.g., social cue perception), which is inferred quickly and largely without contextual integration [76,77]. For example, acute IN-OT increased eye gaze to faces [78], ToM accuracy, temporoparietal junction (TPJ) activity, and TPJ-mPFC connectivity in men with SCZ and schizoaffective disorders [79]. In contrast, IN-OT over several weeks was not associated with improved social cognition [80,81], suggesting acute, but not long-term, IN-OT benefits on SCZ-related social-cognitive dysfunction.[4]

In sum, though there is supporting evidence across healthy and clinical populations that IN-OT in modulates certain social-cognitive processes and related behavior, mixed and null findings also indicate that broader therapeutic efficacy of IN-OT in adulthood has yet to be determined.

2.3. Older Adulthood

Previous work on IN-OT effects in social cognition has almost exclusively examined younger populations. This limited approach, combined with evidence that aging is characterized by decline in some social-cognitive abilities (e.g., emotion perception and attribution; [82–84]) that are known to be affected by IN-OT [8], as well as growing support that the OT system may change with age[5], has resulted in recent calls for the examination of IN-OT's social-cognitive effects among older adults [7,8,85].

As summarized in reviews, preclinical evidence regarding age-related change in the endogenous OT system is mixed [8,85] and still rather limited in humans [1]. However, there is first evidence indicating that advanced age, particularly in males, may be associated with a (numerical) decline in plasma OT levels [86,87], OT-immunoreactive neurons [88,89], and receptor binding [90]. Hormonal systems that interact with the OT system [91,92], such as cortisol [93] and estrogen [94], have also shown to affect social cognition in aging [85].

The impact of advanced age on OT signaling with relevance to social-cognitive capacities is unknown [1]. It is possible, however, that age-related changes to these coordinated endogenous systems contribute to interindividual variation in social cognition and response to IN-OT. For example, there is emerging evidence of age- and/or age-by-sex-related differences in IN-OT modulation of emotion recognition and meta-mood [27,28]. It is possible that because older adults differ from younger adults in physiological, cognitive, and socioemotional domains they may experience greater benefits from IN-OT [1,8]. Moving forward, a better understanding of the links between age-related change in endogenous systems and IN-OT social-cognitive response is needed [85,95].

The few existing IN-OT studies to date have generated some encouraging results on social-cognitive benefits in healthy older adults. In particular, acute IN-OT enhanced facial emotion recognition in older men; with no effects among older women [27]. Similarly, IN-OT enhanced self-reported meta-mood [28] and (trend-wise) functional amygdala-mPFC

[4]For a review on IN-OT in SCZ see [137].
[5]For reviews on the effects of aging on the OT system see [1,7,8,85].

coupling in older men (but again not in older women) [29]. Furthermore, supporting IN-OT effects on brain response in aging, acute IN-OT resulted in a large-scale amygdalar network in older adults during angry, fearful, and happy dynamic face identification, while older adults in the placebo group recruited a different and smaller amygdalar network [96]. However, there also is work that does not support this pattern of age- and age-by-sex differential findings. In particular, acute IN-OT improved ToM comparably in young and older adults [97] and did not improve perceived facial trustworthiness in either age group [98]. These previous studies focused on acute IN-OT administration. Only one study to date has examined prolonged IN-OT effects (over 10 days) in healthy older adults and found that individuals in the OT group reported less physical functioning decline and fatigue as well as increased gratitude, while no changes were found for mood, cardiovascular states, or social activity [99].

Of note, prior work included generally healthy older adults. Although it is currently unclear if/how the OT system in humans is impacted by pathological aging [1], IN-OT may be a valuable, symptomatic treatment option in dementia [17]. This speculation is based on evidence that prefrontal [100] and medial temporal brain regions (e.g., hippocampus and amygdala) [101] are not only structurally altered [102] and related to social-cognitive impairments in various forms of dementia [103], but also overlap with OT-related projection [104,105] and receptor sites [106,107].

However, to date, only one acute IN-OT study on social cognition comprised older individuals with the behavioral variant of frontotemporal dementia (bvFTD) and reported OT-related reduction in facial anger and fear recognition [17]. Repeated IN-OT furthermore resulted in dose-dependent improvement in a subset of behavioral bvFTD symptoms (i.e., apathy and expressions of empathy) and interactions with caregivers [108]. Future research may benefit from extending investigations to other subtypes of dementia towards the determination of IN-OT effects on social-cognitive decline in pathological aging [9].

Taken together, research on IN-OT and social cognition in older adults is limited and results are mixed, with some promising first findings in healthy and pathological aging. Also, in line with work in younger adults, emerging sex-dimorphic patterns of results suggest possible benefits in older men, but not older women, and support the possibility that gonadal hormones (e.g., estrogen, testosterone) and/or other interindividual variables (e.g., clinical status, social proficiency) are at work.

3. Discussion

3.1. Contextual Factors, Interindividual Differences, and Clinical Status Moderate IN-OT Effects

In summary, the current literature on IN-OT's social-cognitive effects is not yet conclusive, but rather has generated mixed evidence [22] and also several null findings [21]. Meta-analyses furthermore suggest that the magnitude of IN-OT effects are often small [13,23,57,68]. Based on our literature review, it is evident that the observed potential benefits of IN-OT on social cognition across the lifespan are often qualified by moderating contextual factors and interindividual differences.[6]

In particular, contextual factors, such as the specific social-cognitive processes being examined or the stimuli included in experimental tasks, can contribute to variations in findings. For example, OT has been shown to impact prosocial behavior (e.g., trust and empathic behavior) [109] as well as related neurocircuitry in favor of in- vs. out-group members [57,59,110]. An emerging body of null findings and conflicting evidence across social-cognitive domains in both healthy [21] and clinical [23,68] populations indicates that IN-OT response may be more variable than previously speculated [21,25,49]. The use of standardized, validated social-cognitive measures in future studies may ameliorate methodological shortcomings that could have contributed to these variable/null findings and would facilitate direct replication [25,111]. Additionally, extending investigations to include naturalistic stimuli that are more representative of real-life social interactions (e.g., dynamic, multimodal emotion, and social cue displays; [112]) could constitute another crucial step towards determining more generalizable, socially relevant IN-OT modulatory effects. These stimuli would also allow to improve the determination of IN-OT's temporal dynamics during social processing and decision-making [59,113].

Importantly, there is growing acknowledgment in the field, that IN-OT related physiological (e.g., pupil diameter) and neural (e.g., amygdala activation, ERPs) modulation occurs not only for social but also for non-social stimuli [59,114], supporting theories proposing that OT's modulatory effects extend beyond social domains [2,3]. To test these predictions, future experimental tasks can systematically vary stimuli and/or contexts to better assess and distinguish dimensions of salience (e.g., social vs. non-social stimuli) as well as motivational aspects (e.g., threatening vs. non-threatening stimuli) of IN-OT-related processing.

Similarly, the summary of the literature suggests that interindividual differences determine who benefits from IN-OT. For example, IN-OT may be particularly effective in adults with lower social-cognitive proficiency [25] and/or lower endogenous OT levels [8]. Sex may further qualify the modulatory effects of IN-OT on social-cognitive processes and behaviors (e.g., IN-OT related improvements in less socially proficient men [25] and older men [27,28]). Gonadal hormones are known to have co-evolved and interact with the endogenous OT system throughout development [30,85] and the field has recently become more inclusive of women, including investigations on IN-OT modulation of the brain [115,116] and behavior [25].

To better capture interindividual variation in IN-OT effects, studies should measure baseline and post-administration levels of endogenous OT and other hormones (e.g., gonadal hormones, cortisol). In particular, the use of unextracted (vs. extracted) samples in plasma OT assays has received growing support as a reliable measurement [117,118].[7] Along these lines, systematic assessment of baseline levels of social-cognitive proficiency will also be beneficial for adequately assessing change after IN-OT and identifying therapeutically relevant effects [25].

[6]See [138] for a discussion on moderating factors of OT's social-cognitive effects.
[7]See [139] for a recent review that discusses the challenges surrounding current methods for OT measurement.

Our review further identified that clinical status is another factor that impacts IN-OT modulation of social cognition and its therapeutic efficacy. For example, in PWS, IN-OT administration earlier in development may be more beneficial than later [37,39]. This is perhaps due to the endogenous OT system being more malleable in early life [32] or that certain clinical conditions are associated with greater hypothalamic deficiencies (e.g., decreased OT receptors/neurons) in adulthood [37]. This is in line with the notion of potential critical periods for OT-related brain and behavioral modulation [22], but long-term impacts of IN-OT administration in early life, including safety and tolerability, need to be carefully considered. In particular, concerns have been raised, based largely on preclinical evidence, that repeated OT treatment in early development may lead to long-term social impairment in adulthood (e.g., bonding and parental behaviors), potentially in a sex-dimorphic pattern [119].

Taken together, given that there is a dearth of efficacious pharmacological treatments for social-cognitive dysfunction with little to no side effects [66,67], further exploration of IN-OT as an effective and safe treatment is worthwhile. Additionally, because there is evidence of variations in OT response across contexts and individuals/clinical groups, the effectiveness of IN-OT in modulating social cognition needs to be established with special attention to moderating factors towards the development of tailored treatment plans [9,12]. This will require systematic investigations in well-powered, well-controlled, representative samples, covering a wider age range and using rigorous methodology with greater efforts toward preregistration and direct replication [111].

3.2. Moving IN-OT Research Towards an Integrative Human Lifespan Approach

IN-OT research has proliferated largely due to the popularity of initial promising findings on its use to enhance social cognition. However, this initial excitement was tempered as more research brought attention to methodological and conceptual concerns that limited understanding of OT function and modulation of social cognition, especially across development [2,9,49].

As the field evolved, several theories were put forth to increase conceptually driven, mechanistic OT research. For example, the *prosocial hypothesis* [36,120] stated that IN-OT promotes affiliative prosocial behaviors (e.g., trust, empathy) by increasing attention to positive emotions. This view was challenged by the *social salience hypothesis*, which argued that OT increases social salience perception in a context-specific manner, regardless of valence [58,121]. Kemp and Guastella [122,123] put forth the *social approach/withdrawal hypothesis*, which proposes that IN-OT increases salience of both positive and negative stimuli, eliciting approach-related behavior and inhibiting withdrawal-related behavior, respectively. More *interactionist* conceptualizations of OT signaling and exogenous modulation then highlighted contextual, interindividual, and developmental dynamics [1,2,26,113,124].

Finally, very recent frameworks conceptualized IN-OT brain and behavioral modulation to account for social and non-social contexts [3,59]. Of these latter more holistic approaches, the *allostatic theory* [2] most recently proposed that OT is involved in maintaining stability in dynamic environments. According to this framework, OT is involved in the processing of

social and non-social cues throughout development, depending on actual and anticipated contextual demands that align with the promotion of survival. These recent perspectives propose that OT function across social and non-social contexts may be mediated by approach–avoidance motivation [3,59].

Although these recent theoretical conceptualizations of IN-OT effects highlighted the importance of focusing on the impact of IN-OT in a broader range of contexts (not only social contexts), as our review shows, current empirical IN-OT research is still limited in its investigative focus on distinct, isolated phases of the lifespan without considering the dynamic and interrelated nature of human development under various contextual influences [125]. However, importantly, our review supports that IN-OT effects are not unilateral or universal across development, populations, and/or social-cognitive processes and behaviors [9]. We propose that an integrative human lifespan approach (Fig. 1) is warranted to capture the complex, dynamic nature of developmental processes that can impact OT modulation of social cognition [126].

Adopting an integrative human lifespan approach will permit researchers to gain unique knowledge about the role of IN-OT on social cognition within and across life phases, accounting for multi-directionality of effects throughout development. The suggestions for future work proposed next, in the context of our integrative human lifespan approach, has the potential to advance etiological understanding of OT throughout development [2] and push the field towards broader generalization [2,9,127]. Fig. 1 synthesizes current research findings and identifies pressing knowledge gaps across the three distinct lifespan segments reviewed. Based on the observations made in this narrative review, we discuss what we have identified as promising future directions for novel research on IN-OT and social cognition specifically within the context of the proposed integrative human lifespan approach.

Future IN-OT research would benefit from consideration of coordinated physiological, cognitive, and behavioral functions of OT as well as potential interactions of IN-OT with the endogenous OT system throughout development. In particular, in line with the Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin (AGeNeS-OT) [8], using a combination of genetic, neurobiological, and socio-behavioral experimental and clinical assessments will allow for a more comprehensive understanding of IN-OT effects on social cognition across the human lifespan. This includes investigation of baseline physiological (e.g., endogenous OT/hormone levels, genetic profiles, neurobiological responses) and social-cognitive moderators (e.g., emotion identification, ToM, trust) [26,30].

As summarized in Fig. 1, going beyond current practice that examines distinct, isolated age groups outside of their broader developmental contexts, it will be important to design longitudinal (and cross-sequential; [128]) studies that capture inter- and intra-individual (age/cohort) differences in IN-OT effects across the full spectrum of the lifespan, instead of comparisons solely focused on isolated, extreme age groups. This approach will allow for cross-linking throughout the ages, regarding mechanisms of action, efficacy, as well as tolerability/safety. Additionally, it will be crucial to investigate developmentally relevant moderators that can have long-term impacts on endogenous OT levels and sensitivity to IN-OT, like early life adversity [35] and attachment history [30].

To facilitate consistent, age-comparative investigations, moving forward it will be useful to develop validated social-cognitive test batteries; follow standardized OT administration protocols (e.g., dosage, frequency, and duration)[8]; and periodically synthesize existing research following standardized guidelines (e.g., PRISMA; [129]). Future work will also benefit from the implementation of equivalence and Bayesian hypothesis testing to determine the sensitivity and stability of detecting the absence of significant OT-related effects within age groups [21,130].

More research has moved from using acute to repeated administration over time, which better reflects long-term medical treatment and the prolonged capacity often needed to observe pharmacologically inducted change [9]. Thus, in addition to well-controlled, standardized acute studies to determine basic mechanistic processes, more prolonged clinical trials will help determine OT's therapeutic potential for improving social cognition, under consideration of developmental dynamics.

Current research largely examines male individuals, while there is growing evidence suggesting sex- and possibly sex-by-age dimorphism in endogenous OT levels [86,131] and IN-OT effects [25]. This investigative focus on males is indicative of a broader bias of excluding females in clinical/drug response trials [132] due to various factors ranging from sex bias in diagnostic and recruitment criteria (e.g., the primary use of males in ASD-related research [49]) to concern over potential hormonal confounds [133]. Increasing the representation of females in IN-OT research is necessary for producing generalizable findings as well as to allow tailoring of treatment plans. Thus, we propose the use of a-priori powered samples with well-balanced sex ratios to explicitly address sex differences in OT response across the lifespan. Careful tracking of baseline levels of gonadal hormones and endogenous OT will be essential in this context [30], as well as strict control and monitoring of factors that interact with OT levels and function (e.g., use of hormonal treatment, stage of the menstruation cycle, medication intake, etc.).

Also, clinical IN-OT research is limited by a focus on high-functioning individuals, primarily with ASD and SCZ. Efforts to summarize IN-OT findings in clinical contexts typically suffer from the heterogeneity of the studied samples that do not differentiate between diverse clinical diagnoses (e.g., ASD, SCZ, borderline personality disorder, posttraumatic stress disorder, etc.; [23,65,68]). These clinical investigations largely address earlier life phases without much consideration of older samples or developmental dynamics. Extending investigative efforts to less researched clinical populations (e.g., dementia, drug dependence, chronic pain; e.g., [134]), while capturing a wider age range to adequately reflect developmental processes, has potential to clarify IN-OT social-cognitive effects within and across diagnoses over the lifespan [22]. Future work in this context should seek to employ larger placebo-controlled trials and consider investigating a broader range of social-cognitive processes and behaviors (e.g., social decision-making, dynamic emotion identification).

[8]These methodological considerations in the context of repeated IN-OT administration has been extensively discussed in [9,12].

In addition to evidence that IN-OT can modulate physiology in brain regions via nasal pathways [20], recent studies have identified multiple projection sites of OT in the brain [2] along with OT-related connectivity among specific brain regions (e.g., amygdala-prefrontal connectivity [29]; cortico-striatal connectivity [115]; resting-state networks [135,136]; and allocation of attention early in the processing stream [59]). However, the neural underpinnings of OT effects are still poorly understood and largely unexplored in older adulthood and concerning developmental dynamics. Thus, we propose greater incorporation of neuroimaging and electrophysiological methodology to allow for increased multi-method investigations and delineation of brain mechanisms underlying OT's modulation of social-cognitive processes across development.

4. Conclusions

In this narrative review, we synthesized recent evidence on IN-OT and social cognition across the three life phases of early life, young/middle adulthood, and older adulthood, towards our proposal of an integrative human lifespan approach for future IN-OT research on social cognition. We propose that scientific advancement in IN-OT and social cognition research requires an integrative lifespan approach that systematically uses standardized, multi-method, longitudinal, and cross-sequential assessments in well-powered, well-controlled, representative samples. We believe that this approach has the promise to move the field forward by capturing the complex and dynamic nature of IN-OT's modulation of social cognition across the human lifespan, offering more a comprehensive understanding and broader generalizability.

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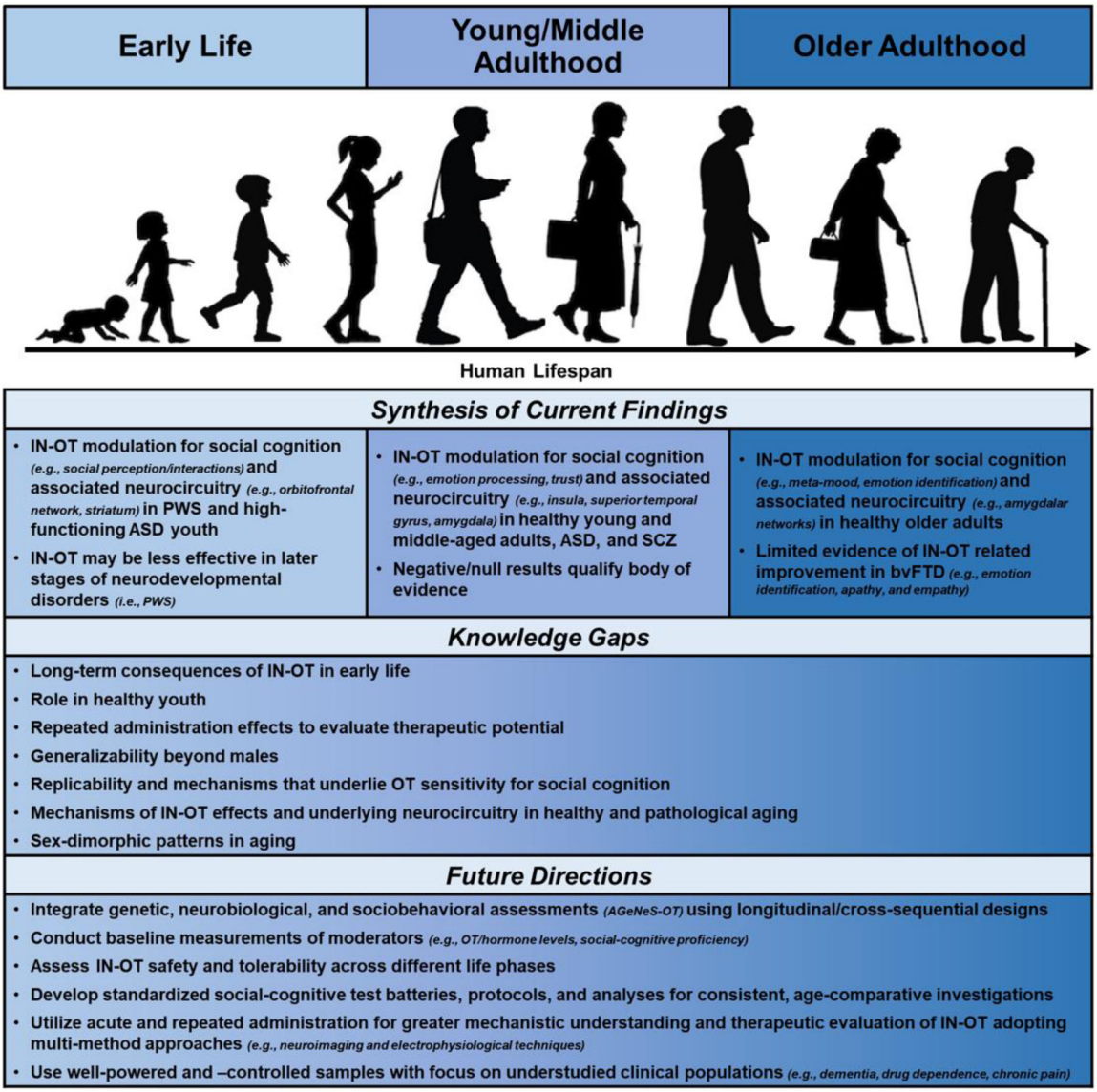

Fig. 1:

Literature Synthesis, Knowledge Gaps, and Future Directions in IN-OT Research on Social Cognition

Note: IN-OT: Intranasal Oxytocin, PWS: Prader-Willi Syndrome, ASD: Autism Spectrum Disorder, OT: Oxytocin, SCZ: Schizophrenia, bvFTD: Behavioral variant of Frontotemporal Dementia, AGeNeS-OT: Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin

Table 1.

Overview of IN-OT research on social cognition in humans (organized by life phase)

Reference	Age (range and/or mean; in years)	Sex	Dosage & Frequency	Regimen & Duration	Design	Main Finding(s)
EARLY LIFE						
PWS (Includes some mixed-age samples)						
Einfeld et al., 2014	12–29; 17.8	M/F	24 and 40 IU (for 16+ year-olds); 18 and 32 IU (for 13–15 year-olds), BID	Repeated, 8 weeks	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased temper outbursts with higher doses; no IN-OT effects on social cognition
Kuppens et al., 2016	6–13.7; 9.3 (median age)	M/F	12, 16, 20, or 24 IU, BID	Repeated, 4 weeks	Double-blind, randomized, placebo-controlled, crossover	IN-OT reduced anger, sadness, conflicts, and improved social behavior in children younger than 11 years; no IN-OT effects in children older than 11 years
Miller et al., 2017	5–11; 8.2	M/F	16 IU, once a day	Repeated, 5 days	Double-blind, randomized, placebo-controlled, crossover	IN-OT improved socialization, anxiety, and repetitive behaviors
Tauber et al., 2017	0.8–5.7 months; 3.9 months	M/F	Step 1: 4 IU, every other day; Step 2: 4 IU, every day; Step 3: 4 IU, BID	Repeated, 7 days	Proof-of-concept, monocentric phase 2 escalating dose	IN-OT improved social withdrawal behavior and mother-infant interactions; increased neural network connectivity correlated with changes in social behavior
ASD in Youth						
Guastella et al., 2010	12–19; 14.88	M	18 IU (for 12–15 year-olds); 24 IU (for 16–19 year-olds), once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT improved emotion recognition
Gordon et al., 2013	8–16.5; 13.2	M/F	12 IU (for 7–11 year-olds); 18 IU (for 12–15 year-olds); 24 IU (for 16+ year-olds), once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased activity for social judgments, but decreased activity for non-social judgments, in regions of the striatum, middle frontal gyrus, mPFC, orbitofrontal cortex, and superior temporal sulcus
Tachibana et al., 2013	10–14.5; 11.93	M	8, 16, 24 IU, BID (increased every 2 months)	Repeated, ~7 months	Open-label trial	IN-OT improved communication and social interactions; no IN-OT effects on other behavioral outcomes
Anagnostou et al., 2014	10–17	M/F	0.2, 0.26, 0.33, 0.4 IU/kg, BID	Repeated, 12 weeks	Modified Maximum Tolerated Dose Open-label trial	IN-OT improved scores and performance in some reassures of social function and social cognition
Dadds et al., 2014	7–16; 11.79 (OT), 10.74 (P)	M	12 IU (for under 40 kg); 24 IU (for over 40 kg), once a day	Repeated, 4 days	Double-blind, randomized, placebo-controlled, between-groups	No IN-OT effects on emotion recognition, social interaction skills, or general behavioral adjustment
Guastella et al., 2015	12–18; 13.85 (OT), 14 (P)	M	18 IU (for 12–15 year-olds); 24 IU (for 16–18 year-olds), BID	Repeated, 8 weeks	Double-blind, randomized, placebo-controlled, between-groups	No IN-OT effects on social behavior
Gordon et al., 2016	8–16.5; 13.16	M/F	24 IU (for 16–19 years); 18 IU (for 12–15 year-olds); 12 IU once (for 7–11	Repeated, 21 days	Double-blind, randomized, placebo-controlled, crossover	IN-OT enhanced connectivity between reward and socioemotional processing related regions especially for social (vs. non-social) stimuli

Reference	Age (range and/or mean; in years)	Sex	Dosage & Frequency	Regimen & Duration	Design	Main Finding(s)
			year-olds), once a day			
Munesue et al., 2016	15–45; 22.5	M	8 IU, BID	Repeated, 8 weeks	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased reciprocal social interactions; no IN-OT effects on core social symptoms
Yatawara et al., 2016	3–8; 6.2	M/F	12 IU, BID	Repeated, 5 weeks	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased caregiver-rated social responsiveness
Parker et al., 2017	6–12; 9.35 (OT), 8.13 (P)	M/F	24 IU, BID	Repeated, 4 weeks	Double-blind, randomized, placebo-controlled, parallel-groups	IN-OT enhanced social abilities, especially among those with the lowest levels of pre-treatment endogenous OT concentrations; no IN-OT effects on in repetitive behaviors or anxiety
YOUNG/MIDDLE ADULTHOOD						
Healthy Populations						
Kosfeld et al., 2005	22	M	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased trust in others
Kirsch et al., 2005	18–40; 26.7	M	27 IU; once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT reduced amygdala activation to fearful faces
Baumgartner et al., 2008	21.7	M	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT reduced fear of social betrayal and activation in regions involved in fear processing (amygdala and midbrain regions) and post-feedback adaptations (dorsal striatum)
Bos et al., 2018	19–24; 20.2	F	24 IU, once	Acute	Placebo-controlled, within-groups	IN-OT was associated with activation in reward and salience processing regions in response to viewing infants' faces
Bartz et al., 2019	18–40; 22.7 (M), 21.6 (F)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT selectively improved empathic accuracy for less socially proficient males (vs. more proficient); no IN-OT effects on empathic accuracy for females
Quintana et al., 2019	20–30; 23.81	M	8 IU intranasally; 24 IU intranasally; 1 IU intravenously, once	Acute	Double-blind, randomized, double-dummy, crossover	8 IU IN-OT reduced pupil dilation and resulted in a positive association with pupil dilation and right amygdala activation when processing social (faces) and non-social (shapes) stimuli; no OT-related effects were obtained for other doses
Tabak et al., 2019	18–31; 20.88	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	No IN-OT effects on various tasks tapping into different constructs (e.g., deception detection, empathy, working memory) and involving various stimuli (e.g., social and non-social)
Sheng et al. (2013)	18–26; 21.88	M	32 IU, once	Acute	Double-blind, randomized,	OT elicited larger ERPs (P2) to painful than neutral faces of racial in-group but not racial out-group

Reference	Age (range and/or mean; in years)	Sex	Dosage & Frequency	Regimen & Duration	Design	Main Finding(s)
					placebo-controlled, within-groups	faces. OT resulted in positive correlation between P2 amplitudes and implicit attitude toward in-group members.
Xue et al., 2020	21.7	M	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT resulted in faster perception and larger pupil dilation for social (vs. non-social) stimuli in an interocular suppression task tapping into conscious visual awareness
Clinical Populations						
ASD						
Anagnostou et al., 2012	18–60; 33	M	24 IU, BID	Repeated, 6 weeks	Double-blind, randomized, placebo-controlled, parallel-groups	IN-OT improved social perception measured by RMET, repetitive behaviors, and emotional well-being
Domes et al., 2013	24 (ASD); 24.3 (HC)	M	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased right amygdala activity to faces
Aoki et al., 2014	22–41, 30.8	M	24 IU, once	Acute	Double-blind, placebo-controlled, crossover	IN-OT increased accuracy for inferring others' social emotions and increased right anterior insula activation
Watanabe et al., 2015	24–43; 32.2	M	24 IU, BID	Repeated, 6 weeks	Double-blind, randomized, placebo-controlled, crossover	IN-OT reduced symptoms relating to social reciprocity and increased resting-state functional connectivity between anterior cingulate cortex and dorsomedial prefrontal cortex
Kruppa et al., 2019	18–26, 21.79 (ASD); 18–25, 22.09 (HC)	M	20 IU, once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT selectively enhanced reinforcement learning associated with social (vs. non-social) stimuli along with increased brain activity in the nucleus accumbens during social (vs. non-social) feedback
Bernaerts et al., 2020	18–35; 25 (OT), 24 (P)	M	24 IU, once a day	Repeated, 4 weeks	Double-blind, randomized, placebo-controlled, parallel-groups	IN-OT was associated with a reduction in self-reported repetitive behaviors and feelings of avoidance towards others; no IN-OT effects on core social symptoms
SCZ						
Guastella et al., 2015	22–57; 37.42	M	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, within-groups	IN-OT enhanced higher-order social cognition performance; no IN-OT effects on general neurocognition
Jarskog et al., 2017	18–65; 41.9 (OT), 36.1 (P)	M/F	24 IU, BID	Repeated, 12 weeks	Double-blind, randomized, placebo-controlled, between-groups	IN-OT improved negative symptoms only in individuals with SCZ but not schizoaffective disorder; no IN-OT effects on social cognition
Bradley et al., 2019	40.3 (SCZ); 39.8 (HC)	M	40 IU, once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased fixation time on the eyes (eye gaze); higher attachment anxiety and greater symptom severity were predictive of greater eye fixation time

Reference	Age (range and/or mean; in years)	Sex	Dosage & Frequency	Regimen & Duration	Design	Main Finding(s)
De Coster et al., 2019	35.3 (SCZ); 27.96 (HC)	M	40 IU, once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT increased ToM accuracy and right TPJ activation during ToM tasks
Lee et al., 2019	44.74 (SCZ); 35.07 (HC)	M/F	20 IU, BID	Repeated, 3 weeks	Double-blind, randomized, placebo-controlled, parallel-groups	No IN-OT effects on social cognition and functioning
PWS						
Tauber et al., 2011	18.7–43.6; 28.5 (median age)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased trust in others and lowered sadness and disruptive behavior; no IN-OT effects on other social skill tests
OLDER ADULTHOOD						
Healthy Populations						
Barraza et al., 2013	60–95; 80.33	M/F	40 IU, once a day	Repeated, 10 days	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased dispositional gratitude and reduced self-reported physical decline and fatigue; no IN-OT effects on social activities/engagement or other affective measures
Campbell et al., 2014	19.68 (YA), 72.07 (OA)	M/F	20 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT improved emotion recognition in older males but not in older females
Ebner et al., 2015	22.4 (YA), 71.2 (OA)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased self-reported attention to own feelings only in older males
Ebner et al., 2016	22.7 (YA), 71.2 (OA)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT increased resting-state amygdala-mPFC connectivity (trend-wise) in older males
Grainger et al., 2018	18–26, 20.18 (YA); 65–90, 73.25 (OA)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, within-groups	IN-OT improved ToM ability irrespective of age
Grainger et al. 2019	18–26, 20.18 (YA); 65–90, 73.37 (OA)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, within-groups	No IN-OT effects on judgments of facial trustworthiness
Horta et al., 2019	18–31, 22.4 (YA); 63–81, 71.2 (OA)	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, between-groups	IN-OT was associated with a large scale amygdalar network in OA for anger, fear, and happiness
Clinical Populations						
Jesso et al., 2011	64.40	M/F	24 IU, once	Acute	Double-blind, randomized, placebo-controlled, crossover	IN-OT associated with reduced recognition of angry faces in patients with bvFTD; IN-OT-related improvement in scores on NPI
Finger et al., 2015	62.1–69.9, 66 (OT); 53.4–69.9, 61.1 (P)	M/F	24, 48, or 72 IU, BID	Repeated, 1 week	Double-blind, randomized, placebo-controlled, parallel-groups	Trends of improvement were observed for the IN-OT group on the measures of apathy and empathy in patients with bvFTD

Abbreviations: ASD: Autism Spectrum Disorder, BID: Twice-a-day, bvFTD: Behavioral Variant of Frontotemporal Dementia, ERPs=Event-related potentials; F: Female, HC: Healthy controls, IN-OT: Intranasal Oxytocin, IU: International Units, M: Male, mPFC: Medial Prefrontal Cortex, NPI: Neuropsychiatric Inventory, OA: Older Adults, OT: Oxytocin, P: Placebo, PWS: Prader-Willi Syndrome, RMET: Reading the Mind in the Eyes Test, SCZ: Schizophrenia, ToM: Theory of mind, TPJ: Temporoparietal Junction, YA: Younger adults.

Note: For regimen, “Acute” refers to the administration of IN-OT as a single dose; “Repeated” refers to the administration of IN-OT in chronic (e.g., daily administration) or intermittent (e.g., administration once every other day or once every week) fashion.