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Review

Intranasal oxytocin, social cognition and neurodevelopmental disorders: A meta-analysis

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ABSTRACT

Deficits in social cognition are pervasive and characteristic of neurodevelopmental disorders (NDDs). Clinical trials of intranasal oxytocin (IN-OT) to improve social cognition have yielded inconclusive results. The current study is a meta-analysis of randomized controlled trials (RCTs) considering the effect of IN-OT on social cognitive domains across a range of NDDs. Medline, PsychINFO and Scopus were searched for RCTs published through to July 25, 2017. Seventeen studies met inclusion criteria, comprising 466 participants with a NDD. Meta-analysis using a random-effects model, revealed that IN-OT had no significant effect on emotion recognition (Hedges' $g = 0.08$), a moderate but non-significant effect on empathy (Hedges' $g = 0.49$), and a small, significant effect on theory of mind (ToM) (Hedges' $g = 0.21$). Meta-regression indicated that the effect of IN-OT on social cognition was not moderated by the diagnosis or age of participants, or the dose or frequency of IN-OT administration. The results highlight a need for more well-designed RCTs, as it remains difficult to draw conclusions about the potential for IN-OT to improve social cognition in NDDs. The promise of IN-OT should be considered tentative.

1. Introduction

Oxytocin (OT) is a neuropeptide primarily produced in the hypothalamic nuclei. It is then transported to the posterior pituitary and released into the blood stream. OT also diffuses into the cerebral spinal fluid (CSF) and travels through the central nervous system (Francis et al., 2014), acting within the brain as a neurotransmitter and neuromodulator (Landgraf and Neumann, 2004; MacDonald and MacDonald, 2010). OT is well known to influence social attachment (Carter, 1998), and promote parental nurturing and social bonding (Young and Barrett, 2015). Accumulating evidence indicates that OT also plays a role in human social cognition (Hammock, 2015).

Although definitions vary considerably, social cognition generally refers to the multiple integrative mental processes that underlie social interactions (Barbato et al., 2015; Green et al., 2008; Levine et al., 1993). For the purpose of this review, social cognition is conceptualized within the context of the model developed by Adolphs (2001). At the input end, social cognition requires attention to and perception of social stimuli. The complex, integrative interpretation of this information is the core of social cognition. It may be divided into lower-order, automatic processes such as emotion recognition versus higher-order interactive processes that are conscious and controlled (Evans, 2008). These include theory of mind (ToM), the ability to attribute mental states to the self and others (Baron-Cohen et al., 1985), and empathy, the flexibility to make an appropriate emotional response to another's mental state (Abu-Akel et al., 2014).

In healthy adults, a single dose of intranasal oxytocin (IN-OT) increased gaze to the eye region of faces (Guastella et al., 2008a), improved empathic accuracy (Bartz et al., 2010; Guastella et al., 2009), social memory (Guastella et al., 2008b), and ToM (Domes et al., 2007). Different mechanisms have been hypothesized to explain OT's influence on social cognition, including reducing fear (Kosfeld et al., 2005), increasing motivation (Gordon et al., 2011) and enhancing the salience of social information (Bartz et al., 2011). It is likely that these mechanisms are not mutually exclusive, but rather combine or alternate according to individual and contextual factors (Bartz et al., 2011; Preti et al., 2014).

Arising from this development in OT research, interest has turned to its potential application in neurodevelopmental disorders (NDDs) characterized by impairments in social cognition. NDDs are a broad group of conditions caused by disruption in brain development (Thapar et al., 2016), culminating in limitations in intellectual or adaptive behavior (American Association on Intellectual and Developmental Disabilities, 2010; American Psychiatric Association, 2013). Defined by persistent deficits in social communication and interaction, as well as

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by restricted, repetitive patterns of behaviors and interests (American Psychiatric Association, 2013), much of the interest in the application of OT has been directed toward autism spectrum disorder (ASD). Rather than a discrete diagnostic category, ASD is a continuum of traits that are also found in a range of other NDDs. The social deficits characteristic of ASD are also common in Prader-Willi syndrome (PWS), fragile X syndrome (FXS), and Williams syndrome (WS) (Francis et al., 2014). Additionally, there is mixed evidence suggesting that each of these disorders may coincide with dysfunction in the OT system. This suggests a possible common OT pathway that is vulnerable to early brain abnormalities and environmental impact across NDDs (Francis et al., 2014). With diagnostic features typically appearing in early adulthood, schizophrenia is not typically recognized as a NDD. However, the pathology of schizophrenia is considered neurodevelopmental in origin, with cognitive and behavioral symptoms evident during childhood (Fatemi and Folsom, 2009; Lewis and Levitt, 2002). In addition, there is evidence of OT system disruption in individuals with schizophrenia, and impairments in social cognition are a core feature of the disorder (Bartholomeusz et al., 2015). As such, schizophrenia is included for discussion in this review.

Individuals with schizophrenia and ASD have significantly lower concentrations of plasma OT than age- and sex-matched controls (Green et al., 2001; Kéri et al., 2009; Modahl et al., 1998). Modahl et al. (1998) noted that children with ASD did not exhibit the normal developmental increase in OT concentration, and that the most severe social deficits were observed in children with the lowest concentrations. Individuals with PWS exhibit a reduced number of OT-producing neurons in the PVN (Swaab et al., 1995), as well as decreased concentrations in CSF (Martin et al., 1998). In mouse models of FXS, there is also evidence of fewer OT-positive cells in the PVN (Francis et al., 2014). In contrast, individuals with WS, who are characterized by a diametrically opposed profile of hypersociability, gregarious personality, and increased social drive and engagement, display increased basal OT levels which correlate positively with social approach behavior (Dai et al., 2012).

However, an OT-deficit model of social dysfunction in NDDs may be oversimplified. Other studies found no significant differences in plasma OT between ASD and controls (Miller et al., 2013), while another study indicates higher levels in ASD (Jansen et al., 2006). These contradictory findings could relate to variations in intellectual functioning (Jansen et al., 2006), or inconsistent methods of obtaining and analyzing OT samples (Francis et al., 2014). In addition, common methods used to extract and measure OT in plasma may be unreliable, and the correlation between peripherally measured OT and neural activity is unclear (Leng and Ludwig, 2016; McCullough et al., 2013). Nevertheless, a meta-analysis by Valstad et al. (2017) noted that the correlation between peripheral and central OT was greater following the administration of IN-OT when compared to the correlations between peripheral and central concentrations at baseline. Findings from studies investigating peripheral levels of OT in NDDs should be interpreted with caution.

Parker et al. (2014) revealed that plasma concentrations of OT strongly predicted ToM in children with ASD, their unaffected siblings, and unrelated typically developing controls. This suggests that variations in plasma OT are not uniquely characteristic of ASD, but rather may correspond to individual differences in social functioning more generally. The biological mechanisms underlying social cognitive deficits in NDDs and the potential role of OT remains unclear. Despite this, following promising effects of IN-OT in typically developing populations, a number of clinical trials have been conducted in children and adults with NDDs. The results of these trials have been mixed and inconclusive.

A number of reviews and meta-analyses have attempted to summarize the effect of OT on social cognition in different clinical populations, and these have also been largely inconclusive. For example, Ooi et al. (2017) meta-analyzed RCT's examining the effect of intranasal and intravenous OT administration on social cognition in ASD. Although the majority of studies reported significant improvement on social cognition measures following OT administration, meta-analysis revealed a small and non-significant effect overall.

Including studies based on a heterogeneous range of clinical groups, including ASD and schizophrenia, as well as healthy individuals, a meta-analysis by Leppanen et al. (2017) found that a single dose of IN-OT significantly improved emotion recognition, but only in healthy individuals, and with small effect sizes. IN-OT had no significant impact on emotion recognition in the clinical sample. In contrast, another meta-analysis including a range of clinical disorders, found IN-OT to have a significant impact only in those individuals with ASD. The authors suggested that ASD is less influenced by social experience than the other disorders they considered, such as depression and post-traumatic stress disorder. Early life experiences may therefore moderate the effect of IN-OT (Bakermans-Kranenburg and van IJzendoorn, 2013).

Recent reviews highlight a number of other potential moderators that may also influence the effect of IN-OT on social cognition. These include individual differences such as intellectual functioning, age and gender, as well as contextual factors including the presence of social support, dose and frequency of IN-OT administration and selection of social cognitive outcome measures (Bakermans-Kranenburg and van IJzendoorn, 2013; Hofmann et al., 2015). Lack of consideration of these factors in clinical trials may have led to the equivocal conclusions regarding the potential for IN-OT to alleviate social cognitive deficits in NDDs.

Although previous meta-analyses have considered the effectiveness of IN-OT across a range of psychiatric disorders, none have specifically examined its effectiveness in ameliorating social cognitive deficits in NDDs. Given the substantial overlap in terms of symptoms and OT system abnormalities across these disorders, this study set out to determine the overall effect of OT on social cognition across these NDDs. By considering these NDDs together, the study acknowledges the heterogeneity within, and the overlap between diagnostic categories (Thapar et al., 2016). With existing studies using different participants, methodological procedures, and outcome measures of social cognition, this meta-analysis aims to establish why some studies have found encouraging results, while others suggest more limited effects of OT on social cognition in NDDs. By considering the influence of diagnosis, age, dose of IN-OT, frequency of administration and outcome measures on the results of these studies, the present study aimed to more clearly determine which individuals are most likely to benefit from IN-OT administration, and under what circumstances. A comprehensive meta-analysis is critical to evaluate the potential of IN-OT as a treatment for social cognitive deficits in NDDs, which have significant and debilitating consequences for affected individuals.

2. Method

2.1. Literature search

The included studies were identified following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines (Liberati et al., 2009). The electronic databases, Medline, PsychINFO and Scopus were searched for peer-reviewed studies published between the first available year and July 25, 2017. The following search terms were used: autism OR Prader-Willi syndrome OR fragile-X OR schizophrenia OR Williams syndrome AND intranasal AND oxytocin. The reference lists of identified studies were manually searched to identify further potentially relevant published papers.

2.2. Study selection

Two reviewers examined the titles and abstracts of studies yielded by the search. Studies were included if they met the following criteria: 1) published in the English language; 2) in a peer-reviewed journal; 3) involved the administration of intranasal oxytocin; 4) included