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Tri-Phasic Model of Oxytocin (TRIO): A systematic conceptual review of oxytocin-related ERP research

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Abstract

Background—The neuropeptide oxytocin (OT) has been shown to play a role in variety of cognitive and social processes and different hypotheses have been put forth to explain OT's effects on brain and behavior in humans. However, these previous explanatory accounts do not provide information about OT-related temporal modulation in the brain.

Objectives—This paper systematically reviewed intranasal OT administration studies employing event-related potentials (ERPs) and synthesized the existing evidence into a novel conceptual framework.

Methods—Empirical studies, published until February 2020 and cited in major databases (EBSCOhost, PubMed, and Web of Science), were examined in accordance with PRISMA guidelines. To be included, studies had to: (i) employ intranasal administration of OT, as the chemical modulator; (ii) measure ERPs; (iii) be peer-reviewed journal articles; (iv) be written in English; and (v) examine human participants.

Results—The search criteria yielded 17 empirical studies. The systematic review resulted in conceptualization of the *Tri-Phasic Model of Oxytocin (TRIO)*, which builds on three processing stages: (i) perception, (ii) selection, and (iii) evaluation. While OT increases attention irrespective of stimuli characteristics in the perception stage, in the selection and evaluation stages, OT acts as a filter to guide attention selectively towards social over non-social stimuli and modulates prosociality/approach motivation associated with social stimuli.

Conclusions—*TRIO* offers an empirically-derived conceptual framework that can guide the study of OT-related modulation on attentional processes, starting very early in the processing stream. This novel account furthers theoretical understanding and informs empirical investigation into OT modulation on the brain.

Keywords

Oxytocin; ERPs; intranasal administration; attention; social salience; prosociality; approach/withdrawal

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1. Introduction

The neuropeptide oxytocin (OT) constitutes a crucial chemical modulator of cognition and behavior in both animals and humans. Synthesized mainly in the paraventricular and supraoptic nuclei of the hypothalamus, OT axons project to various areas including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, brainstem, and pituitary gland, leading to modulatory effects both centrally and peripherally (Insel, 2010; Quintana, Alvares, Hickie, & Guastella, 2015a).

While early animal research focused on OT effects in pair bonding, sexual reproduction, and maternal behavior (Young & Wang, 2004), more recent studies investigated OT effects on various aspects of cognition (Hung et al., 2017; Piva & Chang, 2018). In humans, OT has been shown to play a role in basic and more complex processes including modulation of visual attention (i.e., eye gaze modulation, Eckstein et al., 2018; Guastella, Mitchell, & Dadds, 2008), facial expression identification (Shahrestani, Kemp, & Guastella, 2013), trust (Nave, Camerer, & McCullough, 2015), social reward (Groppe et al., 2013), and cooperation (De Dreu & Kret, 2016). OT's effects also appear to have clinical implications in developmental (autism spectrum disorder; Andari et al., 2010; Domes et al., 2013) and psychiatric (Cochran, Fallon, Hill, & Frazier, 2014) disorders as well as in healthy (Barraza et al., 2013; Campbell, Ruffman, Murray, & Glue, 2014; Horta, Kaylor, Feifel, & Ebner, 2019a) and pathological (Finger et al., 2015) aging.

Different hypotheses have been put forth to explain the effects of OT. One of the earliest is the *prosocial hypothesis* (MacDonald & Macdonald, 2010; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2007). This hypothesis states that OT increases attention to positive (e.g., happiness) but not to negative (e.g., fear) emotions and thus enhances affiliative prosocial behaviors such as trust, empathy, and altruism. Support for the prosocial hypothesis comes from human research showing an inhibitory effect of OT on the amygdala to negative stimuli (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kirsch et al., 2005). For example, Kirsch et al. (2005) found reduced amygdala activation in response to fearful stimuli following intranasal OT compared to placebo administration, reflecting OT's *anxiolytic properties*, possibly by reducing stress and promoting prosocial behavior.

However, contradictory evidence emerged from studies suggesting that OT increased stress (Eckstein et al., 2014) and protective behavior, including aggression (Bosch, Meddle, Beiderbeck, Douglas, & Neumann, 2005). Shamay-Tsoory et al. (2009), for example, found that OT modulated not only positive but also negative social behavior and emotion. They argued that OT enhances prosocial behavior only when the context involves cooperative and positive emotions. In competitive and aggressive contexts, in contrast, OT promotes aggression and negative emotions. This alternative explanatory account was coined the *social salience hypothesis*, which argues that rather than generally enhancing prosocial behavior, OT increases the perceived salience of social cues in the environment in a context specific manner, regardless of social cue valence (Shamay-Tsoory & Abu-Akel, 2016).

Building on the social salience hypothesis, Kemp and Guastella (2010, 2011) put forward the *social approach/withdrawal hypothesis*. This account states that OT increases salience of both positive (e.g., joy, trust) and negative (e.g., anger, gloating) emotions that elicit approach-related behavior. At the same time, OT inhibits withdrawal-related behavior which serves moving away from negative stimulation (e.g., anxiety). Evidence for this hypothesis was based on studies showing that OT increased recognition of both positive and negative social stimuli (e.g., happy and angry faces; Tollenaar, Chatzimanoli, van der Wee, & Putman, 2013), decreased the experience of social threat (e.g., attenuation of brain activity for aversive stimuli; Petrovic, Kalisch, Singer, & Dolan, 2008), and encouraged approach-related and prosocial behavior (e.g., trust; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005).

An alternative account put forth by Bartz, Zaki, Bolger, and Ochsner (2011) (see also Olff et al., 2013) proposed that the effects of OT on social cognition are not only influenced by contextual factors but also by interindividual variables. This *interactionist model* was based on findings that OT can constrain or amplify social cognition and behavior depending on (i) the context (e.g., experimental task features, in- vs out-group status), (ii) interindividual variables (e.g., sex, personality, age, expertise), and (iii) person–context interactions. For example, participants who received intranasal OT behaved more altruistically toward in-group members but more aggressively toward out-group members, when their own group was threatened with financial loss (De Dreu & Kret, 2016). OT was also shown to increase empathy selectively in less compared to more socially proficient individuals (Bartz et al., 2010).

Finally, recently, Piva and Chang (2018) proposed the *multistage model*. According to this framework OT exerts its effect on multiple stages of the social decision-making process. These stages include sensory perception, valuation, decision formulation, and behavioral output, with possible feedback from each of these stages to one or more previous stage(s) to subsequently impact the next set of computations. Specifically, this model proposes that OT modulates the salience and relative value of stimuli by increasing or decreasing noise at different processing stages, which in turn influences approach motivation and prosocial tendencies. That is, OT simultaneously affects perception and salience of social stimuli as well as the propensity to approach or avoid stimuli as a function of context (e.g., reward present vs. absent; Chang, Barter, Ebitz, Watson, & Platt, 2012) or interindividual differences (e.g., males vs. female rhesus monkeys; Winslow, Noble, Lyons, Sterk, & Insel 2003).

The *multistage model* provides a unifying framework to consolidate existing OT findings. However, assumptions of the model are currently based on intracellular activity recording in animals and functional magnetic resonance imaging (fMRI) in humans without considering evidence from event-related potential (ERP) studies of OT in humans. Thus, in its current form the *multistage model* does not integrate fine-grained information about OT-related temporal modulation in the brain.

1.1. Scope and Aims of the Review

In this paper, we systematically reviewed ERP studies using intranasal OT administration to summarize current knowledge on OT's temporal processes in the human brain and synthesized this literature in the context of a novel conceptual framework, the *Tri-Phasic Model of Oxytocin (TRIO)*. ERPs provide high temporal resolution (on the milliseconds level; see Box 1 for a short description of the ERP technique). To date, the ERP technique has been only rarely used in OT research. There are different methodological approaches to study OT-related effects in humans (see Box 2) and there is an ongoing discussion in the literature as to whether peripheral OT concentrations reliably index central OT levels (Carson et al., 2014; Leng & Ludwig, 2019; Valstad et al., 2017). In addition, there are statistical concerns regarding the power of OT studies leveraging genetic approaches to reliably predict and detect small effects that single nucleotide polymorphisms (i.e., genetic variations) may have on brain functioning and behavior (for a meta-analysis, see Bakermans-Kranenburg & Van Ijzendoorn, 2014). The current systematic review therefore exclusively focused on ERP studies employing intranasal OT administration, which is thought to result in central OT effects (Quintana, Smerud, Andreassen, & Djupesland, 2018).

Specifically, the current review aimed at: (i) improving understanding of temporal characteristics of OT effects in the brain by providing a systematic review of ERP studies using intranasal OT administration; (ii) synthesizing the existing evidence into a novel conceptual framework that can guide the study of OT-related temporal modulation in the brain; and (iii) identifying current research gaps and promising future research directions for the study of OT-related temporal brain dynamics.

2. Methodology

This review was conducted in accordance with PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). The systematic literature search comprised articles published from the first date available to February 2020. We used the keywords “oxytocin” AND “event-related potentials OR ERPs” in EBSCOhost, PubMed, and Web of Science. We also scanned reference lists of the papers found. Details concerning the method of literature search and criteria for inclusion and exclusion of studies are shown in Figure 1. To be included studies had to: (i) employ intranasal administration of OT, as the chemical modulator; (ii) measure ERPs; (iii) be peer-reviewed journal articles; (iv) be written in English; and (v) examine human participants. After removing duplicates and screening abstracts, our search criteria yielded 30 articles. Of the 30 articles, 4 were excluded because they did not record ERPs and 9 were excluded because they did not employ intranasal OT administration (see Table S1 in the supplemental material for an overview of studies pertaining to peripheral OT measures and studies adopting a genetic approach that were identified in our literature search but were not included in our review). The final set included 17 articles using intranasal OT administration (all single dose studies) and ERPs. Table 1 provides an overview of all ERP studies included in this review.

3. Review of OT-related ERP Studies

This section summarizes the results from our systematic literature review regarding ERP studies employing intranasal OT administration (see also Table 1). We have organized major empirical outcomes from short (*100–200 ms*) over middle (*200–300 ms*) to long (*>300 ms*) ERP component latencies towards improved understanding of temporal characteristics of OT effects.

3.1. Short latency (*100–200 ms*)

Both the N170 and the vertex positive potential (VPP) components are associated with the encoding of structural information from faces based on initial processing of facial features (Rossion & Jacques, 2012). These components are also modulated by valence and/or arousal of stimuli (Carretié, Hinojosa, Martín-Loeches, Mercado, & Tapia, 2004).

In a within-subjects design study, 24 IUs of OT (vs. placebo) enhanced N170 amplitude on occipitotemporal electrode sites in mothers during a facial expression categorization task regardless of the age (infant vs. adult) and expression (happy vs. sad) of the facial stimuli (Peltola, Strathearn, & Puura, 2018). Administration of 16 IUs of OT (vs. placebo) in a within-subjects design study resulted in larger VPP amplitudes over central electrodes in women who reported lower maternal love withdrawal for faces presented as feedback in a flanker task irrespective of facial expression (happy vs. disgusted; Huffmeijer et al., 2013; but see Huffmeijer, Tops, Alink, Bakermans-Kranenburg, and van IJzendoorn, 2011 for non-significant effects in the same task with women who applied 24 IUs of OT vs. placebo). These findings suggest that OT-related attentional facilitation occurs irrespective of stimulus characteristics (e.g., valence, facial age) and under different task settings, ranging from simple categorization to more demanding selective attention/inhibition.

However, there are exceptions to the effect of OT-related facilitation operating irrespective of stimuli and task context in short latency ERP components. In particular, 24 IUs of OT (vs. placebo) administration in a within-subjects design study with men resulted in a shorter N170 latency over posterior electrode sites to fearful than neutral faces, suggesting that OT increased processing efficiency for arousing faces (Tillman et al., 2019). Furthermore, in a within-subjects design study with men who applied 24 IUs of OT vs. placebo, OT elicited larger error related negativity (ERN) at frontal and frontocentral electrodes for mistakes in a flanker task that was performed in dyads (vs. individually). In contrast, the placebo elicited similar ERPs for mistakes regardless of whether the task was performed individually or in dyads (de Bruijn, Ruissen, & Radke, 2017). This finding suggests an OT-related increase in error detection, which could have resulted from distress knowing that one's actions may negatively affect another person in the dyadic task context.

Taken together, the current evidence supports that OT may enhance information processing irrespective of stimulus characteristics and task demands in short latency ERP components. Exceptions were arousing stimuli or interactive tasks with high social stakes for which OT facilitated recruitment of attentional resources, such as prioritization of arousing over neutral stimuli or social over individual mistakes. There also is evidence that interindividual differences (e.g., childhood experience) moderate OT-related effects in short latency ERPs.

3.2. Middle latency (200–300 ms)

The N2 component reflects processing of emotional arousal (particularly pleasant-going; Olofsson, Nordin, Sequeira, & Polich, 2008) and response conflict (Yeung, Botvinick, & Cohen, 2004). In a between-subjects design study using 24 IUs of OT vs. placebo, men completed a Go/No-Go task either individually or in dyads (Ruissen & de Bruijn, 2015). Relative to placebo, OT resulted in faster response times and larger N2 amplitudes at fronto-central and parietal electrode sites for Go trials in the dyad compared to the individual condition, possibly reflecting OT-related increase in social processing when responding together with a partner. This finding suggests that OT-dependent increase in middle latency ERPs may be selectively associated with social rather than non-social task contexts. This interpretation is also consistent with the finding that N2 amplitudes in a non-social auditory oddball task did not differ between men who self-administered 40 IUs of OT vs. placebo (Born, Fehm-Wolfsdorf, Lutzenberger, Voigt, & Fehm, 1987).

Another mid-latency component is the P2 (Hillyard et al., 1973) which reflects selective attention and feature processing, such as detailed perceptual analysis of faces (Ebner, He, & Johnson, 2011) as well as empathic neural response to other's pain (Han, 2018). It is particularly sensitive to semantic categorization including self- and other-referential processing (Mu & Han, 2010) and in- and out-group processing (Sheng & Han, 2012). In a within-subjects design study with men, 32 IUs of OT (vs. placebo) reduced the P2 over fronto-central electrodes for self-related personality judgments, but P2 for other-related (well-known celebrity) personality judgments was similar between the drug conditions (Liu, Sheng, Woodcock, & Han, 2013). In addition, this OT effect was stronger in individuals who viewed themselves as being more strongly connected with others (i.e., interconnectedness). These findings suggest that OT may alter the balance between self- and other-referential processing and that an OT-related reduction in self-referential processing may influence understanding of others, with this effect more pronounced in individuals reporting higher levels of interconnectedness. In the context of in- vs. out-group membership, 32 IUs of OT (vs. placebo) resulted in larger P2 at fronto-central electrode sites in response to pain expressions of own-race (Asian) compared to other-race (Caucasian) faces in a within-subjects design study with men (Sheng, Liu, Zhou, Zhou, & Han, 2013). This finding suggests that OT-related facilitation in neural processing related to empathy towards the suffering of in- compared to out-group members.

Taken together, middle latency ERP studies suggest that OT may guide attention by increasing salience of social over non-social task contexts. Importantly, OT may increase attention to self-relevant group membership enhancing empathy towards in- over out-group members. This OT-enhanced neural tuning towards in-group others appears to be moderated by stimulus characteristics (e.g., valence/arousal, facial race), contextual factors (e.g., social vs. individual task setting), and interindividual differences (e.g., sociocultural interconnectedness).

3.3. Long latency (>300 ms)

The later segment of OT effects on ERPs is dominated by the P3 component (also called P3a) which reflects allocation of attention to salient task-relevant stimuli (Polich & Kok,

1995) and higher-order cognitive operations (e.g., updating contents of working memory; Polich, 2007). In a within-subjects design study, non-mothers showed a larger P3 over central electrodes for infant compared to adult faces following 24 IUs of OT (vs. placebo) administration (Rutherford et al., 2017). Focusing on N3, which is another long latency component sensitive to affective processing (Carretié & Iglesias, 1995), in a within-subjects design study with fathers who administered 24 IUs of OT vs. placebo, Waller et al. (2015) found larger N3 for own- than familiar- or unfamiliar-child faces in fathers with insecure attachment following OT administration. This effect was not obtained in fathers with secure attachment who showed similar N3 for all child faces irrespective of familiarity. These findings highlight a role of interindividual differences in OT effects on temporal processing in the context of child-parent attachment during long latency components.

P3 is followed by a positive slow wave denoted as late positive potential (LPP) or P3b which reflects sustained attention toward motivationally significant stimuli (Pehlivanoglu & Verhaeghen, 2019; Schupp, Flaisch, Stockburger, & Junghöfer, 2006) and processes related to semantic evaluation of information (e.g., perspective taking, empathy; Nieuwenhuis, Aston-Jones, & Cohen, 2005). Using a within-subjects design, administration of 24 IUs OT (vs. placebo) elicited greater LPP over parietal electrodes to images containing humans (vs. not containing humans) in healthy men who were sensitive to anticipated punishment and criticism (Althaus et al., 2015). This effect was also evident in men with autism spectrum disorder who were oversensitive to stressful situations (Althaus et al., 2015) and also in those patients who had higher plasma OT concentrations than healthy controls (Althaus et al., 2016). These findings indicate that OT enhances LPP for social over non-social stimuli particularly in some individuals or clinical groups.

The previously mentioned study by Huffmeijer et al. (2013) found larger LPP across centroparietal electrodes in women for both happy and disgusted faces after intranasal OT but not placebo administration. Also, in another previously mentioned study by de Bruijin et al. (2017), placebo elicited decreased ERPs (300–500 ms) for mistakes in social (vs. individual) contexts, while OT elicited similar ERPs in both social and individual contexts. These findings demonstrate that OT effects on LPP are influenced by the arousal level of stimuli and task context (but see Petereit, Rinn, Stemmler, & Mueller, 2019, for a non-significant effect of task context on LPP amplitudes in women who self-administered 40 IUs of OT vs. placebo).

Furthermore, in the previously mentioned study by Liu et al. (2013), OT relative to placebo reduced LPP over fronto-central electrodes for self-referential personality trait judgements, but increased LPP for other-related judgments. This finding suggests that OT effects on LPP are more pronounced for other- than self-related processing. Wu, van Dijk, and Zhou (2013) used 32 IUs of OT or placebo in a between-subjects design study with men who indicated ownership of objects primed with either negative or positive adjectives. While ERPs during the 300–1000 ms window were larger for positive than negative other-owned objects in the OT group, this pattern was reversed in the placebo group. Thus, OT-related facilitation in other-related processing was linked to positive rather than negative valence.

In the context of in- vs. out-group membership, in a between-subjects design study with men and women, 24 IUs of OT vs. placebo increased ERPs (750–1000 ms) over parietal electrode sites, reflecting familiarity-based encoding of own-race (Caucasian) rather than other-race (Chinese) faces during encoding (Herzmann, Bird, Freeman, & Curran, 2013). During recognition, women in the OT vs. placebo group showed larger ERPs (800–1200 ms) at mid-frontal regions reflecting familiarity-based recognition advantage for own- (vs. other-) race. In contrast, men in the OT (vs. placebo) group showed this memory advantage for other- (vs. own-) race faces. More recently, in a between-subjects design study, a group of men who varied in levels of empathy and group membership (i.e., belonging to rival groups in soccer or politics) administered 24 IUs of OT (vs. placebo). They then completed a decision-making task involving distribution of resources to in- or out-group members which in turn resulted in gain or loss of points/resources (Schiller, Domes, & Heinrichs, 2020). ERP data during 200–500 ms time window over posterior electrode sites showed that negative valuation of out-group gains occurred in the placebo group. The OT group, in contrast, showed positive valuation of out-group gains. Importantly, this pattern was only evident in individuals who reported low (vs. high) levels of empathy. These findings suggest that OT eliminated negative valuation processes towards out-group members especially in individuals with low empathy.

Taken together, OT-related increase in sustained attention during long latency ERP components specifically occurs for socially arousing over non-arousing stimuli, possibly reflecting selective semantic evaluation of motivationally significant information. Importantly, OT tends to modulate attentional processes in this late processing stage toward facilitation of other- compared to self-relevant information or group membership, possibly as a reflection of positive evaluations associated with others. OT effects are further modulated by contextual information and interindividual differences.

4. Tri-Phasic Model of Oxytocin (*TRIO*)

Based on our systematic review of OT-related ERP studies in humans, we propose the *Tri-Phasic Model of Oxytocin (TRIO)*. The literature demonstrates that OT-related ERP modulation starts early, remains sustained over time, and occurs across different processing stages. In particular, as depicted in Figure 2, *TRIO* builds on three processing stages: (i) perception, (ii) selection, and (iii) evaluation. Each stage will be introduced in more detail next and discussed in reference to the reviewed literature and in relation to existing hypotheses of OT.

The *perception stage* is reflected in short-latency OT-related modulation (~100–200 ms). According to *TRIO*, in this stage, OT enhances initial perceived salience, possibly regardless of stimulus characteristics (e.g., valence, facial age) and in a variety of contexts/tasks (e.g., from passive viewing to selective attention paradigms) (Huffmeijer et al., 2013; Peltola et al., 2018). Although not included in this systematic review, using genotyping and image valence and arousal ratings in males, more negative N1 to images in *OXTR* rs53576 GG than AA carriers was found irrespective of image content (humans vs. objects) and valence (Choi, Minote, & Watanuki, 2017; see Table S1). This finding indicates that OT-related enhancement in this early processing stage may occur for both social (e.g., faces, images

involving humans) and non-social (e.g., objects) stimuli and is in line with findings from intranasal studies in which OT effects occur irrespective of stimuli characteristics and type of cues. Under some conditions, however, OT prioritizes perception of socially salient information in this stage, namely when the information requires immediate attention (e.g., high arousal stimuli; Tillman et al., 2019; see also Peltola et al., 2014 in Table S1 for shorter N1 latency in response to viewing distressed infant (vs. adult) faces in both mothers (vs. non-mothers) and GG (vs. non-GG) allele carriers of *OXTR* rs53576) or when social stakes are high (de Bruijn et al., 2017).

The observed modulatory effects of OT in the perception stage are not entirely consistent with predictions from the *social salience hypothesis* (Shamay-Tsoory & Abu-Akel, 2016). That is, while the *social salience hypothesis* predicts OT-related enhancement in attention for social over non-social cues, ERP studies suggest that an OT-related boost in attention in this early stage may be independent of stimulus characteristics and may be comparable for social and non-social cues. Moreover, while some studies indicate that OT-related modulation in the perception stage seems to occur mostly based on initial perceived salience, involvement of early processing pertaining to higher-order cognitive processes (e.g., empathy, perspective taking) may factor in under some circumstances (e.g., performing tasks in dyads; de Bruijn et al., 2017) in this early perception stage. Thus, the extent to which ERP effects in this early perception stage can be mapped onto the *prosocial* (MacDonald & Macdonald, 2010) and the *social approach/withdrawal* (Kemp & Guastella, 2010) *hypotheses* is yet to be determined. In contrast, current ERP evidence from the perception stage partially supports the *interactionist model* (Bartz et al., 2011; Olf et al., 2013), in that interindividual differences (e.g., childhood experiences; Huffmeijer et al., 2013) moderate OT-related attentional modulation in this stage, and those modulatory effects may be conditional on stimulus characteristics and contextual factors (e.g., high arousal, high social stakes; de Bruijn et al., 2017; Tillman et al., 2019).

The *selection stage* is reflected in middle-latency OT-related modulation. During this stage, OT guides allocation of attention more selectively to prioritize social over non-social cues (Ruissen & de Bruijn, 2015), possibly by increasing allocation of attention towards self-relevant group membership. For example, OT-induced increase in approach and prosocial tendencies, reflected by enhanced empathy-related neural response in P2 for the suffering of members of the in-group compared to the out-group (Sheng et al., 2013) first appears in this stage. Findings from ERP studies employing OT-related genetic approach support these interpretations. Highlighting the selection of social over non-social cues during middle latency ERP components, Choi et al. (2017 in Table S1), for example, found more negative N2 to images of humans relative to objects in male GG allele carriers of *OXTR* rs53576, while male AA carriers showed the opposite pattern. In the context of inter-group interactions, Luo et al. (2019 in Table S1) reported more inclusive and flexible empathic neural response (P2) toward in-group members in GG compared to AA carriers of *OXTR* rs53576.

Overall consistent with the *social salience hypothesis* (Shamay-Tsoory & Abu-Akel, 2016), *TRIO* proposes that in the selection stage, OT may enhance salience of social over nonsocial stimuli, with stimulus salience modulated by emotional valence and/or arousal. Further, in

line with the *prosocial hypothesis* (MacDonald & Macdonald, 2010) and the *social approach/withdrawal hypothesis* (Kemp & Guastella, 2010), approach and prosocial motivation become apparent during the selection stage in the form of empathy-related neural response favoring close other in-group members. Finally, consistent with the *interactionist model* (Bartz et al., 2011; Olf et al., 2013), OT-related attention facilitation for social stimuli in the selection stage may be influenced by interindividual differences (e.g., sociocultural interconnectedness; Liu et al., 2013) in addition to stimulus characteristics (e.g., facial race; Sheng et al., 2013) and contextual factors (e.g., social vs. individual task; Ruissen & de Bruijn, 2015).

The *evaluation stage* is reflected in long-latency OT-related modulation. During this stage, OT-induced semantic elaboration takes place through increased sustained attention to motivationally salient information. For example, OT effects in this stage become more focused on other-related higher-order cognitive processing (Liu et al., 2013), compared to the selection stage where OT-induced increase in allocation of attention occurs for self-relevant (e.g., in-group) information. Moreover, OT-induced effects favoring other-relevant processing in the evaluation stage were positively rather than negatively valenced (Wu et al., 2013; Schiller et al., 2020). Thus, OT facilitates *approach motivation* (Kemp & Guastella, 2010) and *prosocial* tendency (MacDonald & Macdonald, 2010) in this late evaluation stage, possibly enhancing empathy and perspective taking towards motivationally significant stimuli.

Furthermore, consistent with the *social salience hypothesis* (Shamay-Tsoory & Abu-Akel, 2016), OT-related attention modulation in this late evaluation processing stage occurs particularly for emotionally arousing over non-arousing social stimuli (such as demonstrated in processing of infant (vs. adult) faces in Rutherford et al., 2017). The observed ERP patterns are also in accord with the *interactionist model* (Bartz et al., 2011; Olf et al., 2013), in that OT-related effects in this late evaluation stage, like in the selection phase, are influenced by interindividual differences (e.g., social skills; Althaus et al., 2015, 2016; attachment patterns; Waller et al., 2015; gender, Herzmann et al., 2013), stimulus characteristics (e.g., valence; Wu et al., 2013; also see Fowler et al., 2018 in Table S1 for larger LPP in GG (vs. A) allele carriers of *OXTR* rs53576 for socially threatening (vs. neutral or happy) images), as well as contextual factors (e.g., group relations; Schiller et al., 2020).

Taken together, our systematic review of the current intranasal OT-related ERP literature supported a modulatory role of OT on attention allocation that starts early, is maintained over time, and spans over three processing stages. While OT-guided perceptual scanning of stimuli that occurs very early in the processing stream appears to be independent of cue type or stimuli characteristics, upon detection of significant social stimuli, OT may act as gateway to assure that social over non-social stimuli have priority access for higher level processing, possibly by favoring self-relevant group/close other-related information in the selection stage, followed by other-related information in the evaluation stage.

One important advantage of conceptualizing OT effects in the context of *TRIO* is that it offers a common empirically-derived conceptual framework for OT-modulated attentional

effects, ranging from selective to more sustained forms of attention allocation. Although existing hypotheses provide important predictions to explain OT effects on brain and behavior, these predictions do not speak to the temporal processes of OT modulation (e.g., timing and duration of OT effects). *TRIO*, in contrast, formalizes the temporal dynamics of OT-related modulation in the brain, starting very early in the processing stream and reaching into late processing components. More importantly, the newly proposed *TRIO* framework builds upon a widely accepted conceptualization of attentional effects in ERP research. As touched on briefly in Box 1, this conceptualization posits that the sequence of components following a stimulus reflects the temporal sequence of neural processes tapping into different cognitive subsystems (e.g., early versus late) triggered by the stimulus, beginning with early sensory processes and proceeding through decision- and response-related processes (Luck, Woodman, & Vogel, 2000). Thus, *TRIO* is a first attempt to formalize how attentional effects of intranasal OT may operate in different cognitive subsystems under different task conditions by leveraging excellent temporal resolution of the ERP technique. *TRIO* is empirically derived and theoretically grounded and allows formulating specific research hypotheses that can be tested (confirmed or rejected) in future investigations. Through this process, *TRIO* can be refined, extended, and revised moving forward.

To exemplify, according to *TRIO*, processing appears to become more focused on social over non-social stimuli later in the processing stream, while stimuli characteristics are less prominent earlier in the processing. Thus, it is plausible that OT-related modulation may be more automatic in the earlier processing stages and become more controlled later on. To investigate this possibility, future research could employ selective attention or dual-task paradigms and determine (i) whether OT-guided attentional effects occur independent of the availability of attentional resources and (ii) whether these effects are further modulated by processing stages. If the magnitude of OT-related ERP patterns at different processing stages change based on availability of attentional resources as predicted by *TRIO*, then varying task demands to manipulate required attention allocation could be useful in determining the extent to which OT shifts automatic vs. controlled processes across the processing stream. Depending on the results, *TRIO* could be further refined and extended to account for variations in OT-related ERP patterns as a function of the availability of attentional resources at different levels of processing. If, however, the magnitude of OT-related ERP patterns proves to be similar throughout processing regardless of the availability of attentional resources, then the stagewise structure of *TRIO* should be revisited and modified to account for less variation in OT-related processing throughout the processing stream. Thus, *TRIO* can be advanced in the future via a gradual iterative process involving rigorous hypothesis testing. A selection of important research avenues based on *TRIO*'s basic assumptions towards uncovering functional significance of OT-related temporal dynamics in the brain are discussed next.

5. Leveraging *TRIO* in Future Research

Based on our systematic review of OT-related ERP research and our literature synthesis in conceptualizing *TRIO*, we have identified promising future research directions with potential to advance theory and empirical understanding of OT's temporal dynamics in the brain. Next, we will briefly discuss select future research suggestions.

5.1. Interrelations Between Processing Stages

Given the scarce literature base, it is not possible at this point to determine whether the three processing stages proposed in *TRIO* operate in isolation or in tandem throughout the processing stream. In fact, while some studies suggest that OT-related ERP effects may occur sequentially (de Bruijn et al., 2017; Liu et al., 2013), other studies support that the processing stages may overlap and/or interact (Sheng et al., 2013; Ruissen & de Bruijn, 2015). Thus, it is plausible that OT-related modulation in ERPs is sequential, with an initial perceptual scanning of stimuli in the perception stage, followed by more specialized processing operations in the selection and evaluation stages. However, it is also possible that the distinction between the stages become less distinct with OT, resulting in increased overlap and/or interaction between the stages. *TRIO*-guided research to refine propositions regarding temporal sequencing and interactions among the stages will advance theory and enhance empirical understanding of OT effects. Future ERP studies could, for example, systematically manipulate stimulus aspects (e.g., social nature vs. arousal level) within a task context or vary required processing depth or task complexity (e.g., simple categorization vs. social decision making) to enhance understanding of the interrelations between the processing stages as a function of OT.

5.2. Differentiation of Types of Social-Cognitive Information

According to *TRIO*, OT boosts processing of information, maybe irrespective of type of cue or stimuli characteristics in the perception stage, while processing appears to become more focused on social over non-social stimuli in the selection and evaluation stages; with a possible prioritization of self-relevant group/close other-relevant information in the selection phase (Sheng et al., 2013), and a prioritization of other-relevant information in the evaluation stage (Liu et al., 2013; Schiller et al., 2020; Wu et al., 2013). A between-subject design fMRI study with men who self-administered either 40 IUs intranasal OT or placebo showed overlap in cortical regions involved in processing of trait judgments describing self and close-others (i.e., one's mother) in the OT group, but resulted in distinct brain regions for these two conditions in the placebo group (Zhao et al., 2016). This finding further supports that OT may reduce the distinction between self and others, particularly close others. *TRIO* supports a possible OT-guided shift in attentional focus from self or close-others to others throughout the processing stream. Building on this framework, future studies could benefit from multimodal imaging (e.g., ERP and fMRI) combined with behavioral assessment to follow up on this initial proposal of temporal specifics for different types of social stimuli, with the goal to disentangle self- and other-relevant processing and to identify mechanisms of action underlying OT's temporal gating of different types of social information.

5.3. Interindividual Differences and Stimulus/Context Variations

Interindividual differences can impact OT's modulation of temporal aspects in all three processing stages (Althaus et al., 2015, 2016; Huffmeijer et al., 2013; Liu et al., 2013), while variations of OT modulatory effects on temporal dynamics by stimulus characteristics and contextual factors primarily take place during the selection (Ruissen & de Bruijn, 2015) and evaluation (Schiller et al., 2020) stages, and only under some circumstances during the

perception stage (high arousing and high social stakes stimuli; de Bruijn et al., 2017; Tillman et al., 2019). Embedding future research in *TRIO* offers to systematically determine conditions under which OT modulation is affected by interindividual variables in interaction with stimulus/contextual factors along the processing stream. This line of research could be fruitful to identify individual and subgroup responsiveness to OT modulation on temporal aspects under specific circumstances (i.e., stimuli and/or task contexts). For example, there is growing evidence of age- and age-by-sex related changes in the OT system (Campbell et al., 2014; Ebner, Maura, Macdonald, Westberg, & Fischer, 2013; Horta et al., 2019b; Plasencia, Luedicke, Nazarloo, Carter, & Ebner, 2019). However, findings regarding age and sex moderation on OT-related modulation is mixed. For example, while Kirsch et al. (2005) found reduced amygdala activation to fearful faces in men following intranasal OT administration, Domes et al. (2010) found an opposite effect in women. Also, while Campbell et al. (2014; see also Ebner et al., 2015) reported age-differential OT effects pertaining to emotion identification, Grainger et al. (2018) found no age-related benefit of OT on social-cognitive abilities. Of note, only one OT-related ERP study examined effects of sex (Herzmann et al., 2013) and no study to date considered age effects. Thus, future research is needed on OT-modulated attention allocation within *TRIO* that incorporates age- and sex-heterogenous samples.

5.4. Leveraging OT's Temporal Dynamics Beyond Social Processes

TRIO predicts that OT increases perceived salience and facilitates processing, possibly irrespective of type of cue (social vs. non-social) or stimuli characteristics (e.g., valence, arousal) earlier in the processing stream (i.e., the perception stage). This prediction is consistent with recent perspectives which conceptualize OT-related modulation in brain and behavior to account for both social and non-social contexts (for reviews, see Hahari-Dahan & Bernstein, 2014; Quintana & Guastella, 2019). Specifically, a recent re-conceptualization of the *social-approach/withdrawal hypothesis* (aka *general approach-avoidance hypothesis of oxytocin*; Hahari-Dahan & Bernstein, 2014) posits that OT exerts its effect on a variety of personally relevant and emotionally evocative circumstances that range from social (e.g., interpersonal relationships, bonding) to non-social (e.g., survival and adaptation-related situations, such as sensations of pain and thirst) contexts. Furthermore, this position suggests that the broad range of social and non-social effects of OT may be mediated by its action on approach-avoidance motivation and behavior. This modified conceptualization highlights OT's modulatory role on behavior beyond social contexts and the influence of motivational processes (i.e., one's motivational state and the motivational significance of stimuli) on OT effects.

Our systematic review suggests that early OT effects may be independent of type of cue or stimulus characteristics. We furthermore conclude that, only in later processing phases, OT effects may become more specific to socially arousing stimuli or task contexts. In these later stages, higher order-cognitive processes including selective attention (selection stage) and evaluation of motivational significance (evaluation stage) come into play. Of note, in its current form, *TRIO* does not provide any predictions as to whether non-social but motivationally-relevant stimuli or contexts result in OT-related ERPs in the selection or evaluation stage. Rather it proposes that OT-guided processing favors social over non-social

stimuli during later stages of processing. Future OT-related ERP studies will benefit from experimental designs that systematically vary task stimuli and/or context to better capture (and possibly dissociate) social (social vs. non-social) as well as motivational (motivationally significant vs not; stimuli relevant of survival vs. not) aspects of OT-related processing and help to describe their temporal dynamics; with new findings providing the basis for further specification of *TRIO*.

6. Limitations

Like other field of research fields, the literature on OT-related ERP effects is affected by analytical flexibility across studies and publication bias, which impact comparability across studies as well as conclusions drawn. Concerning the ERP technique, for example, some common practices for quantifying (e.g., using mean vs. peak amplitudes; a-priori vs. post-hoc selection of electrode sites and time windows) and analyzing (e.g., risk of inflating Type-I error rates via multiple comparisons) can lead to very high rates of significant-but-bogus effects (Luck & Gaspelin, 2017). Also, the literature on intranasal OT administration has increasingly highlighted the importance of standardized methodology (Guastella et al., 2013; Quintana et al., 2015b) but agreed-upon-guidelines have not yet been consistently implemented (Horta et al., 2019a; Leng & Ludwig, 2016). There also have been growing concerns about statistical reliability and reproducibility of intranasal OT administration studies (Lane, Luminet, Nave, & Mikolajczak, 2016; Quintana, 2018; Tabak et al., 2019; Walum, Waldman, & Young, 2016). Moving forward research on OT's temporal dynamics using ERP will benefit from following research standards and recommendations for increasing methodological rigor in OT administration (Horta et al., 2019a; Leng & Ludwig, 2016; Walum et al., 2016) and implementing agreed-upon ERP research and analysis practices (such as suggested by the Society for Psychophysiological Research; Keil et al., 2014). Furthermore, adopting an open science model by pre-registering study procedures and predictions to optimize transparency and counter publication bias (Munafò et al., 2017) has potential to move the field forward in a consistent and methodologically rigorous fashion.

Currently little is known about anatomical sources of the observed OT-related ERP effects in the brain. Only Sheng et al. (2013) and Liu et al. (2013) have identified potential neural generators of ERP activity associated with OT. In particular, focusing on self-relevant processing (Liu et al., 2013) and group membership (Sheng et al., 2013), these studies found that OT-related ERPs in the P2 time window were generated in the anterior cingulate and medial prefrontal cortex. This finding is consistent with both previous source localization studies focusing on neural generators of the P2 component (Carretie et al., 2004) and projection sites of OT in the brain, including prefrontal cortex, hippocampus, amygdala and sensory cortices (e.g., Knobloch et al., 2012; Maejima et al., 2014; Quintana & Guastella, 2019). Recent fMRI studies have also reported OT-related facilitation in connectivity between distinct neural regions (e.g., amygdala-prefrontal connectivity, Ebner et al., 2016; cortico-striatal connectivity, Bethlehem et al., 2017) as well as OT-induced change in large-scale neural resting networks (Xin et al., 2018; Brodmann, Gruber, & Goya-Maldonado, 2017). However, to date, there are no OT studies examining neural generators of ERPs

systematically by varying stimuli characteristics (social vs. non-social) throughout the processing stream.

A separate line of research focusing on neural sources of ERPs has consistently identified contribution of sensory cortices (e.g., occipito-parietal and occipito-temporal areas; Herrmann & Knight, 2001) as well as centro-parietal (Keil et al., 2002; Sabatinelli et al., 2007) and frontal (Carretie et al., 2004; Holmes et al., 2003) sites to the generation of both early (e.g., P1, N1) and later (e.g., LPP) ERP components, especially when motivationally significant and/or affective stimuli are present (LeDoux, 2000; Vuilleumier, 2002). Thus, it is plausible that, irrespective of the processing stage, ERPs reflecting non-social effects of OT are generated by involvement of sensory cortices, while ERPs that are more specific to social effects of OT originate from large-scale neural networks including brain sites implicated in non-affective (i.e., sensory cortices) and affective (e.g., amygdala, prefrontal and parietal cortex) processing. These brain response patterns may be further moderated by interindividual differences, as suggested by a recent study showing OT-related increase in resting-state EEG activity of neural networks associated with social processing particularly in individuals with high anxiety levels (Schiller, Koenig, & Heinrichs, 2019). Currently, there is not sufficient evidence to draw connections between ERPs and their anatomical sources in the context of OT effects, so the reflections offered here are speculative. Future source localization studies via dense-array EEG recordings or multimodal integration of ERPs and fMRI, for example, will shed light on spatial characteristics of OT-related ERPs.

7. Conclusions

In this paper, we systematically reviewed and synthesized the existing OT-related ERP literature towards development of a novel conceptual framework, *TRIO*. Going beyond previous models and hypotheses, *TRIO* proposes that OT modulation occurs in three processing stages — perception, selection, and evaluation — and offers a theoretical approach that can guide the study of OT-modulation on attentional processes, starting very early in the processing stream and reaching into late processing components. This newly proposed model has the potential to spur future research on OT's temporal dynamics in the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1:**Description of the ERP technique**

ERPs represent the synchronous activation of electrical fields associated with the activity of a large population of neurons in response to sensory, motor, cognitive, affective, etc. events (Fabiani, Gratton, & Federmeier, 2007; Luck, 2005). Specifically, ERPs reflect the summed activation of excitatory postsynaptic potential and inhibitory postsynaptic potential elicited by a stimulus or response. The ERP technique has a poor spatial resolution, but it is very sensitive to real-time neural processes, providing temporal resolution on the scale of milliseconds.

ERPs are characterized in terms of latency (delay of appearance after an event), direction (positive or negative), amplitude (amount of voltage change), and topological (scalp) distribution (frontal, occipital, parietal, etc.) of the components. ERP measurements quantify the amplitude (in microvolts) and latency (in milliseconds) of the waveform associated with a specific stimulus or response. The ERP recording yields several components that provide information about neural processing stages, including both early sensory (i.e., perceptual and attentional operations) and later (i.e., high-level cognitive processing) stages.

Box 2:**Measures of OT effects in humans**

OT is released both into the central nervous system (CNS) and into the peripheral circulation from neurosecretory cells in the paraventricular and supraoptical nuclei of the hypothalamus, where most endogenous OT is synthesized. Central and peripheral compartments of the OT system are separated anatomically by the blood-brain barrier (Neumann & Landgraf, 2012). OT level and function cannot be imaged yet, but there are various approaches in humans to measure and/or modulate the OT system centrally.

- One approach is to measure **endogenous peripheral OT concentrations** in blood (Feldman, Weller, Zagoory-Sharon, & Levine, 2007), urine (Seltzer, Ziegler, & Pollak, 2010), or saliva (Carter et al., 2007) and to correlate concentration levels with brain response (Lancaster et al., 2015) and behavior (Feldman, Gordon, & Zagoory-Sharon, 2011).
- Another approach is to determine **central OT concentrations in the CNS by performing lumbar punctures** (Kagerbauer et al., 2013). This approach is highly invasive.
- **OT can be exogenously administered via nasal spray** (Guastella et al., 2013; Quintana et al., 2015a; Striepens et al., 2013), based on evidence that this route of application allows OT to circumvent the blood-brain-barrier (Born et al., 2002; Quintana et al., 2018). There is evidence from animal studies showing increased central OT levels after intranasal administration (Lee et al., 2018; Smith, Korgan, & Young, 2019).
- Some studies have focused on **genetic variation in the oxytocinergic system**, such as related to OT receptor genes (e.g., *OXTR* reflecting OT receptor, *CD38* reflecting OT secretion). For example, GG allele carriers of *OXTR* rs53576 show higher sensitivity to social cues than A allele carriers (AA/GA) (Kogana et al., 2011). Also, CC carriers of *CD38* rs3796863 show improved processing of socially relevant stimuli compared to A allele carriers (AA/AC) (Sauer, Montag, Wörner, Kirsch, & Reuter, 2012).
- Finally, OT can be measured and/or modulated via: examining distribution of OT receptors within the human **postmortem** brain (Mazurek, Beal, Bird, & Martin, 1987); **topical gel** which affects the area of application locally potentially by increasing cell proliferation (Torky et al., 2018); **intravenous (IV) administration**, with subsequent action across the blood-brain barrier (Hollander et al., 2003).

Highlights

- Systematic conceptual review of oxytocin-related ERP studies in humans
- Novel framework on oxytocin's temporal dynamics in the brain
- Oxytocin modulates attention allocation in three processing stages
- Impact of oxytocin on cognition starts early and is maintained over time
- Future directions to advance theory and research of OT's temporal modulation

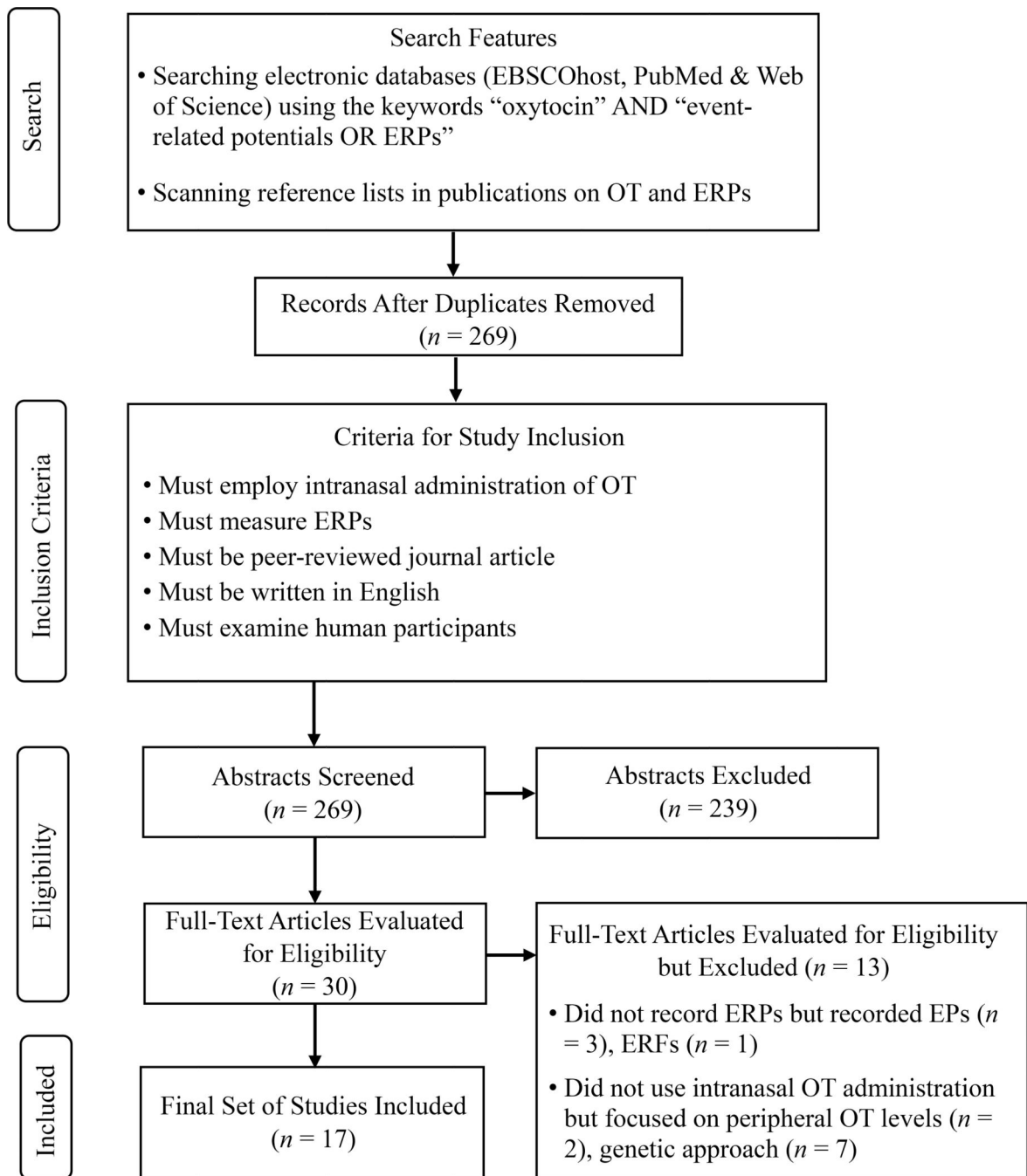


Figure 1. PRISMA flow chart for the search and inclusion/exclusion criteria for studies in this review. *Note:* OT = Oxytocin; ERP = Event-related potential; EP = Evoked potential; ERF = Event-related field

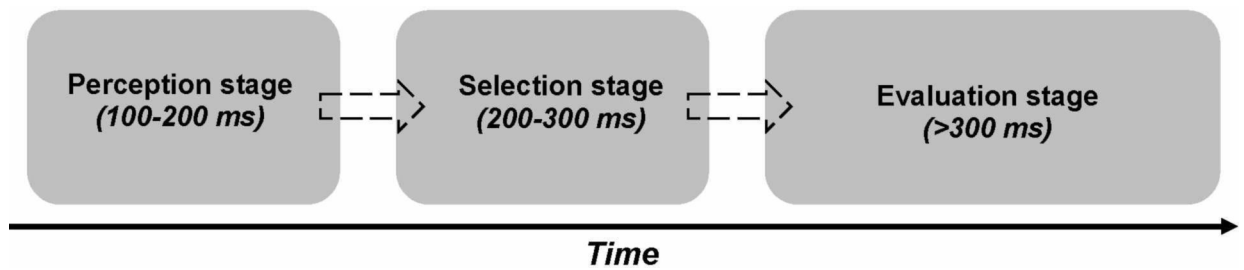


Figure 2.

The *Tri-Phasic Model of Oxytocin (TRIO)*. OT-related modulation on attention allocation starts early, remains sustained over time, occurs across three processing stages: *perception*, *selection*, and *evaluation*. During the short-latency *perception stage*, OT enhances initial perceived salience, possibly by increasing allocation of attention irrespective of stimuli characteristics and type of cues. During the middle-latency *selection stage*, OT guides allocation of attention more selectively to prioritize social over non-social stimuli, possibly by increasing allocation of attention towards self-relevant group membership/close others. During the long-latency *evaluation stage*, OT-induced semantic elaboration takes place through increased sustained attention to motivationally salient information, reflected in a greater focus on other-related higher-order cognitive processing. Interindividual differences impact OT's temporal aspects in each processing stage. While OT effects during the selection and evaluation stages differ qualitatively depending on stimulus characteristics or contextual factors, such modulatory effects occur only under some circumstances in the perception stage. Dashed arrows depict potential interrelations between processing stages throughout the processing stream. Box length reflects time window associated with the processing stage.

Table 1:

ERP research using intranasal OT administration (organized by latency)

Study (year)	Female/ Male (F/M)	Age (range or mean in years)	Sample size	Dosage	Design	Task	Latency in ms (ERP component if applicable)	Main findings
Peltoia et al. (2018)	F	20–40	38 (mothers)	24 IU	Within	Facial emotion categorization task (happy and sad faces of infants vs. adults)	120–220 (N170); 300–600(LPP)	N170: OT (vs. P) elicited larger ERPs, regardless of facial age and emotion.
Huffmeijer et al. (2011)	F	18–30	27	24 IU	Within	Eriksen Flanker task with emotional feedback (happy and disgusted faces)	140–180 (VPP); 300–450 (N400)	No treatment effect on ERPs.
Huffmeijer et al. (2013)	F	18–30	48	16 IU	Within	Same task as in Huffmeijer et al. (2011)	140–180 (VPP); 400–800 (LPP)	VPP: OT (vs. P) elicited larger ERPs for faces in participants reporting lower maternal love withdrawal. LPP: OT (vs. P) elicited larger ERPs for faces.
Tillman et al. (2019)	M	19–32	21	24 IU	Within	Expt.1: Passive viewing of faces (fearful vs. neutral) Expt.2: Passive viewing of neutral faces	72–110 (P1); 110–210 (N170); 200–300 (EPN)	N170: OT (vs. P) elicited shorter latency to fearful than neutral faces in Expt.1. No treatment effect on ERPs in Expt.2.
de Bruijn et al. (2017)	M	18–30	24	24 IU	Within	Eriksen Flanker task (individual vs social context)	0–200 (ERN); 150–250 (Early Pe); 300–500 (Late Pe)	ERN: OT elicited larger ERPs for mistakes occurred in social (vs. individual) contexts. P elicited similar ERPs in both contexts. Late Pe: P elicited decreased ERPs for mistakes occurred in social (vs. individual) contexts. OT elicited similar ERPs in both contexts.
Ruissen et al. (2015)	M	18–35	63 (31 OT, 32 P)	24 IU	Between	Go/No-Go task (individual vs social context)	225–275 (N2); 300–500 (P3)	N2: OT (vs. P) elicited larger ERPs for Go trials in the social than the individual context.
Born et al. (1987)	M	22–33	17	40 IU	Within	Auditory Oddball task	180–360 (N2); 280–460 (P3)	No treatment effect on ERPs
Liu et al. (2013)	M	18–30	20	32 IU	Within	Trait judgment task	80–120 (N1); 220–280 (P2); 520–1000 (LPP)	P2: OT (vs. P) reduced ERPs for self-referential traits. LPP: OT (vs. P) reduced ERPs for self-referential traits but increased ERPs for traits with reference to others.
Sheng et al. (2013)	M	18–26	16	32 IU	Within	Facial race categorization task (painful or neutral Asian vs. Caucasian faces)	84–116 (N1); 140–180 (N170); 128–188 (P2); 200–300 (N2); 400–700 (P3)	P2: OT (vs. P) elicited larger ERPs to painful than neutral faces of racial ingroup but not racial out-group faces. OT (vs. P) resulted in positive correlation between P2 amplitudes and implicit attitude toward in-group members.
Rutherford et al. (2017)	F	18–31	24	24 IU	Within	Passive viewing of houses, infant, and adult faces	149–225 (N170); 200–400 (P3); 300–600 (LPP)	P3: OT (vs. P) elicited larger ERPs for infant than adults faces.

Study (year)	Female/ Male (F/M)	Age (range or mean in years)	Sample size	Dosage	Design	Task	Latency in ms (ERP component if applicable)	Main findings
Waller et al. (2015)	M	30–50	24 (fathers)	24 IU	Within	Passive viewing of child faces (own vs. unfamiliar)	90–140 (P1); 142–200 (N170); 210–300 (P2); 300–350 (N250); 350– 400 (N3)	N3: P elicited more negative ERPs for own-child than familiar-child or unfamiliar-child faces. This own-child effect disappeared under OT in fathers with secure attachment.
Althaus et al. (2015)	M	18–34	61 (30 HC; 31 ASD)	24 IU	Within	Passive viewing of images of humans and scenes	600–1000 (LPP)	OT (vs. P) elicited larger ERPs to pleasant images with humans than those without human in ASD patients who were oversensitive to stressful situations and in HC who were sensitive to criticism and punishment.
Althaus et al. (2016)	M	18–34	61 (30 HC; 31 ASD)	24 IU	Within	Same task as in Althaus et al. (2015)	600–1000 (LPP)	OT (vs. P) elicited larger ERPs for images with humans than without humans only in men with higher plasma OT levels in the ASD group.
Petereit et al. (2019)	F	24	90 (45 OT, 45 P)	40 IU	Between	Cyberball game (social vs. nonsocial context)	800–1400 (LPP)	No treatment effect on ERPs.
Herzmann et al. (2013)	F & M	18–28	52 (26 F; 13 OT, 13 P; 26 M; 13 OT; 13 P)	24 IU	Between	Facial race encoding and recognition task	100–132 (P1); 140–184 (N170); 188–272 (P2); 300–500; 500–800; 750–1000; 800–1200	750–1000 ms: Larger ERPs reflecting encoding advantage for own- (vs. other-) race faces in OT (vs. P) group. 800–1200 ms: Larger ERPs reflecting recognition memory advantage for own-race faces in women in OT (vs. P); in contrast, other-race effect was found for men in OT (vs. P).
Wu et al. (2013)	M	20–25	46 (24 OT; 22 P)	32 IU	Between	Object ownership categorization task (self vs. other)	300–1000	OT resulted in larger ERPs for positively than negatively valenced other-owned objects; P resulted in the reversed pattern.
Schiller et al. (2020)	M	18–39	86 (43 OT; 43 P)	24 IU	Between	Decision-making task resulting in gain vs. loss for in-vs. out-group members	200–500	OT (vs. P) reduced negative valuation of out-group gains; this pattern was only evident in participants with low (vs. high) empathy.

ASD=Autism Spectrum Disorder; HC=Healthy controls; ERN=Error related negativity; ERP=Event-related potentials; IU=International unit; Pe=Error positivity; LPP=Late positive potential; P=Placebo; OT=Oxytocin; VPP=Vertex positive potential

Note: Design column indicates whether OT was a within- or between-subjects design factor.