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Ageing and Oxytocin: A Call for Extending Human Oxytocin Research to Ageing Populations – A Mini-Review

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Abstract
Interest in oxytocin has increased rapidly over the last decades. Consequently, quite a number of studies have addressed the influence of oxytocin on social stress, perception, cognition, and decision making in healthy adults as well as in clinical samples characterized by some form of social disturbance. Surprisingly little research on oxytocin has focused on ageing populations. This is particularly striking in two areas of study: the role of oxytocin in grandparents' behavior toward and bonding with their grandchildren and the effects of oxytocin on the neurocognitive processing of socioemotional stimuli. The current mini-review offers an overview of the literature on the involvement of oxytocin in parental behavior and neurocognitive functioning, and discusses the relevance of these findings to ageing individuals. As the literature shows that oxytocin is profoundly involved in parenting and in bonding throughout life, it is highly likely that oxytocin plays a role in grandparenting and bonding between grandparents and grandchildren as well. However, results obtained with younger adults may not be directly applicable to older individuals in yet another type of relationship. The possibility that age-related changes occur in the oxytocin system (which is at present unclear) must be taken into account. In addition, ageing impairs neurocognitive processes that are profoundly affected by oxytocin (including some aspects of memory and emotion recognition) and is associated with alterations in both structure and function of the amygdala, which is prominently involved in mediating effects of oxytocin. Research investigating the ageing oxytonergic system and studies focusing on the involvement of oxytocin in socioemotional neurocognitive processes and social behavior in elderly individuals, including grandparents, are therefore urgently needed.

Interest in oxytocin has increased rapidly, both inside the scientific community and among the general public. After its initial discovery as an uterus-contracting hormone in the 1950s, the facilitative effects of oxytocin on sexual and reproductive behaviors were soon discovered. In subsequent decades research interest spread to an increasing array of social behaviors. Today, oxytocin is best known as the 'love hormone' among the general public, reflecting its positive effects on affiliation and bonding, but oxytocin has been found to facilitate a wide range of processes and behavior, varying from, e.g., parental care

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to recognizing emotional expressions [1]. Similarly, researchers have observed prosocial effects of oxytocin using diverse experimental setups ranging from computerized games [2] to naturalistic requests for a donation to charity [3]. However, study populations have not been as varied, as the vast majority of studies have focused on relatively young adults. With the current review, we hope to inspire researchers to change this biased focus and to turn their attention to ageing populations.

Oxytocin is a neuropeptide that is synthesized in magnocellular neurons of the supraoptic and paraventricular nuclei (PVN) of the hypothalamus that project to the posterior pituitary from which oxytocin is released into the bloodstream. In addition, neurons in the PVN project to various limbic, mid-, and hindbrain structures (e.g., hippocampus, amygdala, and nucleus accumbens) containing oxytocin receptors. Within the brain, oxytocin can act both as a neurotransmitter and as a neuromodulator [1]. In mammals, oxytocin is well known for its role in parturition and lactation, is involved in the regulation of the hypothalamic-pituitary-adrenal axis, and facilitates reproductive and maternal behavior, infant attachment, and social behavior [1].

A growing body of research suggests that in humans too oxytocin plays a role in mother-infant bonding as well as in parenting behavior [4–7], and that early interpersonal experiences may be important for shaping the oxytocin system [8]. A number of excellent reviews of the literature regarding the involvement of oxytocin in human social behavior and cognition have appeared over the last few years (e.g., [1]). These reviews have addressed the influence of oxytocin on social stress, perception, cognition, and decision making in healthy adults as well as in clinical samples characterized by some form of social disturbance. Oxytocin has been found to attenuate stress responses in social situations (decreasing both levels of cortisol and subjectively experienced anxiety), to facilitate maternal behavior and mother-infant bonding, to promote trust and generosity toward an opponent, to improve emotion recognition and the ability to infer the mental state of another individual, and to facilitate memory for salient social stimuli [1; for meta-analytic evidence regarding the role of oxytocin in emotion recognition and interpersonal trust, see 9].

Given that with ageing substantial changes occur in social networks and relationships as well as in neurohormonal systems [10], surprisingly little research on oxytocin has focused on ageing populations. Studies on oxytocin and ageing could include many interesting topics, such as romantic relationships, neuroendocrine responses to stress, socioemotional well-being, loneliness, and bereavement, as well as potential therapeutic applications. However, for the purpose of the current mini-review we limit ourselves to some of the most salient and pressing issues; the lack of investigations focusing on older individuals is particularly striking in two areas of study. First, even though a myriad of animal studies and a growing number of human studies have focused on the role of oxytocin in parental behavior and bonding, to the best of our knowledge no human studies to date have looked at the role of oxytocin in grandparents' behavior toward and bonding with their grandchildren. Second, there is a rapidly expanding literature about the effects of oxytocin on the neurocognitive processing of socioemotional stimuli. Because with ageing substantial changes occur in brain architecture and chemistry [10, 11], studies among ageing populations are particularly needed. The current mini-review offers an overview of the literature on the involvement of oxytocin in parental behavior and neurocognitive functioning, and discusses the relevance of these findings to ageing individuals. One caveat should be made here: the current mini-review focuses mainly on healthy ageing, and the influence of age-related disease factors is outside the scope of the current paper (apart from some attention to Alzheimer's disease). Nevertheless, researchers interested in the role of oxytocin in elderly participants should always be cautious regarding potential influences of age-related disease in the elderly. In fact, it may be useful for initial studies to focus exclusively on healthy ageing individuals, avoiding potential confounding influences of age-related disease factors. Subsequent studies could then profit from the knowledge gained and focus directly on the impact of age-related disease.

Parenting, Bonding, and Attachment

Compared to the extensive body of research on the involvement of oxytocin in maternal behavior and bonding in animals (particularly rodents), human research is relatively scarce though increasing rapidly. Human studies have related variation in the oxytocin receptor gene (restriction site 53576) to mothers' sensitive responsiveness toward their toddlers [4] and in several studies associations have been found between peripheral oxytocin concentrations and measures of parenting and bonding. In (soon-to-be) mothers, increases in plasma oxytocin concentrations over the course of pregnancy have been found to predict greater attachment to the unborn baby [6] and

levels of oxytocin in blood plasma during both the first trimester of pregnancy and the first month postpartum have been found to be positively related to maternal behavior toward the newborn infant, such as gaze at the infant's face, 'motherese' vocalizations, and affectionate touch [5]. In fact, physical touch may be an important factor in mediating some of oxytocin's effects, being an integral part of both sexual, romantic, and parent-infant interactions [12]. In addition, levels of salivary and plasma oxytocin have been positively related to parenting behaviors of both mothers and fathers of young infants, as well as to the parents' attachment relationships with each other, the infant, and their own parents [13].

The kind of parenting behaviors facilitated by oxytocin may differ subtly between fathers and mothers. For example, Gordon et al. [14] measured mothers' and fathers' plasma oxytocin levels during the first weeks postpartum and approximately 6 months later. Parents' oxytocin levels increased over this period and maternal and paternal oxytocin were positively correlated at 6 months. Maternal oxytocin was related to affectionate parenting behaviors, whereas paternal oxytocin was related to stimulatory parenting behaviors. The effects of oxytocin on fathers' behavior with their young children (1.5–5 years old) have also been demonstrated experimentally. After intranasal administration of 24 IU of oxytocin, fathers provided more structure to their child's play and showed less hostile behavior than after placebo administration [7].

The studies cited above thus suggest that oxytocin is involved in parenting behavior in both fathers and mothers, and point to the importance of oxytocin for parent-child bonding. There is also evidence that oxytocin is involved in other close relationships. It is interesting to note that in the studies on the relation between oxytocin and bonding higher oxytocin levels are not always associated with more positive outcomes. As a stress hormone (possibly functioning to decrease anxiety and facilitate coping behaviors in stressful social settings [1]) oxytocin may be released when concerns about the attachment relationship predominate, as is, for example, the case when relationship distress is high [15]. In addition, effects of oxytocin on memories or representations of a specific relationship may be moderated by attachment style [16].

Taken together, the lines of evidence cited here suggest substantial involvement of oxytocin in parents' behavior with their infants and young children, as well as in various kinds of attachment relationships (whatever the exact direction of the effects). It is therefore definitely possible that oxytocin is also involved in the grandparent-grandchild [or grandparent-parent-(grand)child] relationship. However, to the best of our knowledge, no studies focusing on grandparents have been conducted yet, and it may be unwise to directly extrapolate results to older individuals in yet another type of relationship. The possibility that effects of oxytocin may partially depend on an individual's accumulated attachment experiences [3, 8, 16, 17] and that age-related changes occur in the oxytocin system and/or the neural circuitry underlying oxytocin's behavioral effects must be taken into account. This will be discussed in more detail below, but we first turn to the role of oxytocin in neurocognitive processes thought to mediate effects on socioemotional behavior.

Neurocognitive Processes

Behavioral Studies

Oxytocin has been implicated in various social cognitive processes, including memory, emotion recognition, and the perception and judgment of socioemotional information. Recent evidence suggests that oxytocin selectively improves memory for social stimuli. Notably, oxytocin has been found to improve recognition memory for faces, both when oxytocin is administered before [18] and after [19] the initial learning stage, suggesting an effect of oxytocin on memory consolidation. Oxytocin may facilitate memory encoding specifically for positive facial expressions [20]. Several studies describe facilitative effects of oxytocin on the processing of facial expressions that may underlie the improvements in memory described above. A substantial number of studies have shown that intranasally administered oxytocin improves participants' ability to recognize facial expressions [see 9, for meta-analytic evidence], although there is some inconsistency regarding differential effects for different emotional expressions, complicated by variation in study designs and outcome measures.

On a cognitive level, oxytocin has been found to improve the ability to make inferences about the mental state of another both when observing human interactions [21] and from the eye region of the face, in particular for those who are less emotionally/socially competent [22]. Interestingly and in accordance with the latter findings, oxytocin increased both the number of fixations and the total time of fixation at the eye region of faces in a study by Guastella et al. [23], suggesting that oxytocin increases attention to the eye region of faces (although these findings have not been replicated by other authors yet). Evidence also suggests that effects of oxytocin on the pro-

cessing of the socioemotional content of stimuli are not limited to emotional expressions. Positive (but not negative) sexually themed and relationship-related words that were gradually revealed by a disappearing mask were recognized faster after intranasal oxytocin compared to placebo administration [24].

Imaging Studies

Taken together, behavioral studies suggest that oxytocin facilitates the processing of socioemotional information, possibly via attentional mechanisms. The neural circuitry underlying the cognitive-behavioral effects has been the topic of a number of investigations using fMRI to image brain activity. These studies typically find reductions of amygdala activation among male participants in response to facial expressions (regardless of the emotion displayed) after oxytocin compared to placebo administration. This has been suggested to reflect reduced arousal resulting from a reduction in uncertainty about the meaning of social stimuli due to more efficient processing or processing biases induced by oxytocin [25]. In addition to reduced amygdala activity, reduced functional coupling between the amygdala and regions of the brainstem that mediate fearful behavior and arousal has been observed after oxytocin administration [26]. A slightly more complicated picture is presented by Gamer et al. [27], who distinguished between different subregions of the amygdala. They found that oxytocin decreased activity in anterior parts of the amygdala when viewing fearful faces, but increased activity in these parts in response to happy faces. Increased activity in the posterior amygdala and enhanced coupling between the posterior amygdala and superior colliculus were related to increases in reflexive eye movements toward the eye region of the facial stimuli after oxytocin compared to placebo administration, in accordance with the role of these regions in reflexive shifting of attention.

In contrast to typical results in men, oxytocin increased activity in the left amygdala in response to fearful faces among women. In addition, oxytocin increased activity in brain areas associated with the processing of faces and facial expressions, including the superior temporal cortex (for fearful faces), inferior frontal gyrus (for happy and angry faces), and fusiform gyrus (for happy and fearful faces), suggesting heightened processing of emotional facial expressions after oxytocin compared to placebo administration [28]. However, reduced amygdala activity in response to different kinds of socioemotional stimuli, e.g. infant sounds, has also been observed among female participants. For example, reductions in amygdala activity in response to infant crying were observed in females, together with increases in activity in the insula and inferior frontal gyrus, areas that are connected to and involved in the control of the amygdala [29].

Although there are some inconsistencies regarding the exact nature of effects of oxytocin, the amygdala does seem to be an important locus for oxytocin to exert its effects. This is hardly surprising given the abundance of oxytocin receptors in this brain area [1]. Moreover, genetic variation in the oxytocin receptor (causing oxytonergic transmission to vary in efficiency or effectiveness) has been associated with variation in amygdala volume [30]. Effects of oxytocin on amygdala activity have also been found using interactive paradigms. Reduced amygdala activity after oxytocin compared to placebo administration was observed in male participants while they received painful stimulation of their hand (a needle prick), but, surprisingly, not when they watched a needle prick to their female partner's hand [31]. Baumgartner et al. [2] collected fMRI data while participants performed a trust game. After participants learned that the partner they were playing with was unreliable (reciprocating trust in only 50% of cases), those who had received oxytocin did not decrease their trusting behavior. These participants showed reduced activation of the amygdala, midbrain regions, and the dorsal striatum. Studies like this one provide a link between changes in amygdala activity and prosocial effects of oxytocin.

To summarize, the extant literature points to profound influences of oxytocin on social cognition, heightening the processing of socioemotional information, and improving the perception of and memory for this information. Results regarding eye movements [23] and differential involvement of subregions of the amygdala [27] suggest that attentional mechanisms may be involved, and neuroimaging studies indicate a prominent involvement of the amygdala in mediating effects of oxytocin.

To be able to judge the extent to which these findings are relevant for ageing populations, it is necessary to take into account potential age-related changes in social cognition, in the amygdala, and in the oxytocin system. In general, social-cognitive abilities seem to be relatively little affected by ageing, but a specific decline in emotion recognition (e.g. recognizing emotional facial expressions and emotional prosody), particularly for negative emotions, has been observed in several studies [32]. As one of the best documented effects of oxytocin is improvement in emotion recognition [see 9 for meta-analytic evidence], this may be especially relevant for older individuals.

Ageing

Ageing and Oxytocin

Only a handful of studies have investigated effects of ageing on the human oxytocin system. Furthermore, these studies have relied exclusively on postmortem examinations of neural tissue of the PVN and supraoptic nuclei. In one study, evidence of reduced numbers of oxytonergic cells in the PVN of elderly subjects was found [33], but others found no changes in the number or size of oxytonergic cells [34]. Postmortem studies of brain tissue of elderly persons who suffered from Alzheimer's disease have obtained similarly mixed evidence, with some authors finding evidence suggesting decreased oxytonergic activity [35] and others failing to find such evidence [34]. Animal studies of the ageing oxytonergic system are also comparatively scarce, but age-related changes in circulating levels of oxytocin have been observed, e.g. in rhesus macaques [36]. Studies of ageing rats have used more variable approaches to investigate age-related changes in the oxytonergic system. These studies have obtained evidence for an age-related decrease in central oxytonergic activity, including blunted oxytocin responses to stress [37] and reductions in the number of oxytocin receptors in various brain areas [38], but effects of exogenously administered oxytocin on social memory and depressive-like behavior seem to be preserved in ageing rats [39].

Thus, although studies of rats have provided substantial evidence for age-related decreases in oxytonergic activity, human studies have so far provided mixed evidence. In addition, there are age-related changes in hormonal and neurotransmitter systems interacting with the oxytonergic system, in particular decreased levels of gonadal steroids and decreased dopaminergic activity [10], which might have functional consequences for the oxytocin system. It is clearly too early to draw any firm conclusions regarding the effects of age on the human oxytonergic system and additional research using more diverse methodologies (including the study of oxytonergic activity in living human participants) is needed. It is important to note, however, that even if ageing would adversely affect the human oxytonergic system, this does not necessarily mean that the oxytonergic system is no longer involved in social behavior and social cognition or that effects of exogenously administered oxytocin would disappear [39].

Ageing and the Amygdala

Amygdala volumes decrease with healthy ageing, which could indicate some decline of function of this brain area [11]. In addition, although (peak) responses of the amygdala to emotional stimuli do not change with ageing, there is evidence that the connectivity between the amygdala and other brain regions may be different in ageing individuals. Specifically, in older compared to younger adults connectivity between the amygdala and frontal regions involved in cognitive control and emotion regulation (e.g., anterior cingulate cortex) is enhanced, whereas connectivity between the amygdala and posterior, more perceptual regions (e.g., visual cortex, parahippocampal gyrus) during emotional processing is weakened. This suggests that older individuals recruit different neural circuits and may be using different, more cognitive, information-processing strategies when confronted with socioemotional material than younger adults. These changes in amygdala structure and connectivity may be at the heart of the decline in emotion recognition observed in elderly participants [40]. In participants suffering from Alzheimer's disease enhanced amygdala responses to facial stimuli, correlated with symptoms of irritability and agitation, have been observed, and amygdala volumes were found to be reduced even more than in healthy elderly adults [41].

Amygdala structure and function (as evidenced by connectivity) are thus affected by ageing. Therefore, effects of oxytocin, whether generated internally or administered exogenously, on the amygdala in the elderly may not be identical to those in younger adults. Regarding exogenously administered oxytocin, researchers should be cautious about the possibility for age-related changes in the transport of oxytocin to the brain. However, oxytocin is usually administered intranasally to human participants. This bypasses the vascular system and blood-brain barrier [42], and thus potential changes in drug transport due to ageing of the vascular system are similarly circumvented. Also, the evidence cited above suggests that older individuals may recruit different processing strategies than younger adults, which may be differentially affected by oxytocin. No matter how much research on the ageing oxytonergic system is still needed, the available evidence clearly points to substantial changes in the neural circuitry mediating oxytocin's effects, limiting the generalizability of findings to ageing populations.

Conclusions

Consistent with the primary role of oxytocin around birth and the facilitative effects of this neuropeptide on maternal behavior and bonding in non-human mam-

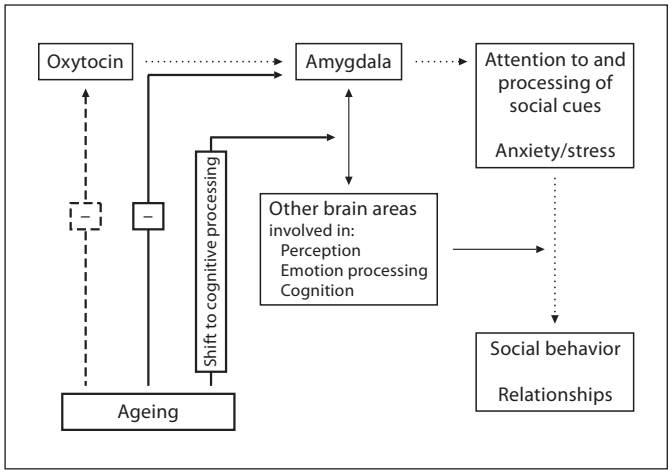

Fig. 1. A model of ageing and oxytocin. Effects of oxytocin on the amygdala, interacting with other brain areas involved in perception (e.g., visual cortex), emotion processing (e.g., limbic and temporal areas), and cognition/cognitive control (e.g., frontal areas, anterior cingulate cortex), play an important part in attention to and the processing of social cues, and in decreasing stress responses and anxiety. Human studies have provided mixed evidence for age-related decreases in oxytonergic activity (bold dashed arrow). Amygdala volumes decrease with ageing. In addition, there is evidence for age-related changes in connectivity of the amygdala to other brain regions during emotion processing, suggesting that older individuals recruit different, probably more cognitive, systems for socioemotional processes than do younger adults (bold solid arrows). These changes in amygdala structure and connectivity are associated with a decline in emotion recognition observed in elderly participants. Whether and how these age-related changes affect the role of oxytocin in social cognition and behavior is currently unknown (dotted arrows). Research investigating the ageing oxytonergic system and studies focusing on the role of oxytocin in socioemotional neurocognitive processes and social behavior in elderly individuals, including grandparents, are urgently needed.

mals, the available evidence suggests that oxytocin is also extensively involved in human parental behavior (with infants and young children) and bonding. Given that many grandparents maintain (close) relationships with their grandchildren and may be actively involved in their grandchildren's lives [43], it is surprising that no research has yet been conducted on the role of oxytocin in grandparenting and grandparent-grandchild bonding. As oxytocin has been shown to be profoundly involved not only in parenting and bonding throughout life, but also in human social behavior toward non-kin [1, 9], it is highly likely that oxytocin plays a role in grandparenting and bonding between grandparents and grandchildren as well. Caution is warranted though, as results obtained with younger adults may not be directly generalizable to elderly populations.

In this context it is also interesting to speculate about the evolutionary underpinnings of oxytocin. Given the extensive involvement of oxytocin in parturition and lactation, sexual and reproductive behavior, and mother-infant bonding across mammalian species (mentioned above), oxytocin likely evolved within the context of reproduction, facilitating both reproduction itself and infant survival. Possibly through the same mechanisms that promote reproduction and mother-infant bonding (e.g., decreasing anxiety and promoting trust toward conspecifics, and facilitating the processing of socioemotional cues) oxytocin also affects human social behavior more generally. Although facilitation of social processes and behavior may be argued to have promoted survival at least in ancient times, oxytocin may still be active after the reproductive years, when it is no longer 'evolutionary useful'. However, to the extent that grandparents may promote infant survival, effects of oxytocin within this period of life may again be of evolutionary importance.

Among the neurocognitive processes affected by oxytocin, memory for salient social stimuli and the recognition of emotional expressions figure prominently. In fact, it has recently been suggested that the primary role of oxytocin may be to increase the salience and processing of emotional information and that the way in which this ultimately affects higher-order cognitive processes and behavior may at least partially depend on contextual factors, including a person's accumulated (socioemotional) experiences [17], and in particular their experiences of warmth or rejection with their parents [8]. In addition to the potential role of contextual and personal factors, the fact that both memory and emotion recognition, in particular the recognition of negative expressions, are adversely affected by age [32] may have consequences for effects of oxytocin in ageing humans.

Neuroimaging studies point to a prominent involvement of the amygdala in mediating effects of oxytocin, which is not surprising given that the amygdala receives extensive input from oxytonergic neurons in the PVN [1]. As mentioned above, extensive changes in amygdala circuitry may occur with ageing. There is evidence for age-related reductions in amygdala volumes and, although responses of the amygdala itself seem to be unaffected by ageing, for age-related changes in connectivity of the amygdala to other brain regions during emotion processing. This suggests that older individuals recruit different, probably more cognitive, systems for socioemotional processes than do younger adults. Besides changes in the

neural circuitry mediating (some of) oxytocin's effects, age-related reductions in gonadal steroid levels and neurotransmitter signaling (in particular that of dopamine) that regulate and/or interact with oxytonergic signaling have also been observed [10].

Whether and how these neural, strategic, and hormonal changes may affect the role of oxytocin in (and change the effects of exogenously administered oxytocin on) social cognition and behavior, including grandparenting and grandparent-grandchild bonding, is currently unknown and hard to predict. Figure 1 provides an overview of the path through which oxytocin ultimately affects social behavior and summarizes current knowledge about effects of ageing on the different components of this path as well as those points that still need to be investigated. As can also be gleaned from figure 1, research investigating the ageing oxytonergic system and studies focusing on the involvement of oxytocin in socioemotional neurocognitive processes and social behavior in elderly individuals, including grandparents, is urgently needed. Interested researchers have a wide variety of methods and strategies at their disposal, including measures of oxytocin levels in bodily fluids (plasma, saliva, urine, CSF), imaging methods, and postmortem investigations of brain tissue to study the ageing oxytocin system, as well as designs in which levels of circulating oxytocin and/or oxytocin administration are related to neuroimaging, cognitive, and behavioral measures to shed light on the role of oxytocin in elderly individuals. As experiments with intranasally administered oxytocin have been rather successful in studies on younger adults we recommend this approach for the study of the influence of varying oxytocin levels on neural and behavioral functioning in the elderly, with the added advantage of causal interpretations.

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