A Meta-Analytic Review and Experimental Study Exploring Links between Aggression and the Oxytocinergic System in Mice and Human Populations

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ABSTRACT

A Meta-Analytic Review and Experimental Study Exploring Links between Aggression and the Oxytocinergic System in Mice and Human Populations

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Interpersonal aggression is a significant source of individual and societal distress. For this reason, countless research projects have attempted to identify the biological and psychological determinants of aggressive behaviour. An emerging body of literature suggests that the nonapeptide oxytocin (OT), generally regarded as a facilitator of prosocial behaviours, can instead amplify aggression and hostility under certain contexts. The current dissertation was designed to clarify the association between OT and aggression, by investigating this relation in both animal and human samples. In the first study, we conducted a systematic meta-analysis of genetic OT-knockout animal-model studies. Relative to genetically unmodified controls, OT receptor knockout mice were found to exhibit significantly elevated aggression, across all behavioural paradigms and outcome measures. Other forms of genetic modification were found to be less reliably associated with subsequent aggression, suggesting that prenatal OT exposure plays a critical role in the development of aggressive behaviour in adulthood. Evidence of contextual and individual variability was also observed. In the second study, we investigated the association between exogenous OT administration and a form of cognitive bias that may be predictive of future aggressive behaviours: autobiographical memory retrieval biases. We found that, under placebo, high-aggression participants exhibited greater difficulty retrieving specific memories of positive events. Following OT administration, the retrieval of specific memories for positive cue words was selectively improved in high-aggression individuals. Additionally, such individuals rated the emotional valence of their autobiographical memories less negatively under OT, when compared to placebo. Importantly, these findings were exclusive to memories retrieved within a social

context. Recollections produced in a non-social environment were rated less positively following OT administration, exclusively for high-aggression participants. These findings again suggest important individual and contextual variability and highlight the potentially deleterious effects of OT administration in the absence of social contact. Together, these studies indicate that OT does modulate the frequency of aggressive behaviours, as well as the cognitive biases that may precede them. Critically, these data also highlight important developmental, individual, and contextual considerations, which in turn allows us to identify viable targets for future research.

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Table of Contents

List of Figures

List of Tables

Chapter 1: General Introduction

Interpersonal aggression is a significant source of individual and societal distress. From the social isolation and psychological anguish that emerges from bullying to the incalculable personal losses that more severe forms of violence force upon victims and their families, aggression is a hazard to us all. Beyond the scope of individual suffering, which itself should not be understated, is the tremendous cost that violence and aggression incurs upon the wellbeing of nations. Loss of productivity, incarceration, and increased strain on medical and judicial services are just some of the expenses that stem from interpersonal aggression. In fact, the societal costs of violent crime are estimated to be roughly 13 billion dollars a year in Canada (Department of Justice, 2021), and the global costs of war and violence are estimated to exceed 14 trillion dollars annually (Broom, 2021). For these reasons, a comprehensive understanding of the biological, psychological, and social underpinnings of violence is vital. While many different approaches to this question merit consideration, one recent avenue of research has produced particularly unexpected findings. Oxytocin (OT) – a peptide hormone traditionally associated with prosocial behaviour and maternal care – has instead been found to increase hostility and competitiveness in certain contexts (e.g.: De Dreu et al., 2012). Given OT's well-established effects on a wide range of social behaviours across a broad variety of species, this peptide represents an especially viable approach to understanding and addressing aggression.

The goal of this thesis is to elucidate the relation between OT and aggression, using two distinct methodological approaches across two unique populations. First, we will perform a systematic meta-analysis of genetic OT-knockout animal-model studies. Contrasts between different types of genetic manipulations will allow us to investigate the contributions of fetal versus lifespan OT availability; contrasts between different behavioural paradigms will further

allow us to examine unique patterns of individual and contextual variability. Second, we will expand upon this biological model to explore the effects of exogenous OT administration on a form of cognitive bias that may contribute to subsequent aggression: autobiographical memory biases. Atypical patterns of autobiographical memory retrieval have been associated with both externalizing (e.g.: Neves & Pinho, 2015; Neves & Pinho, 2018) and internalizing (e.g.: Gibbs & Rude, 2004; Rawal & Rice, 2012) problems and are theorized to directly relate to such issues by shaping self-perceptions and self-schemas (e.g.: Sumner, 2012). Together, these projects will allow us to evaluate OT's role in both biological and psychological risks for aggression.

Oxytocin

Produced in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, the nonapeptide OT was originally most recognized for its role in reproductive and maternal behaviour in mammals (Carter, 1998; Gimpl & Farenholz, 2001). It plays a direct role in childbirth by stimulating the contractions required for parturition (Fuchs et al., 1982; Fuchs et al., 1981). It is also a necessary trigger for milk production (Soloff et al., 1979; Svennersten-Sjaunja & Olsson, 2005) and maternal grooming behaviours in rodents (Amico et al., 2004; Pedersen & Boccia, 2003).

Effects on Prosocial Behaviour

More recently, researchers have found that OT plays a broader role in regulating a wide range of social behaviours in animals and humans alike (Bartz & Hollander, 2006; Campbell, 2010; Ross & Young, 2009). In animals, increases in either endogenous or exogenous OT facilitates pair bonding in monogamous species (Insel & Hulihan, 1995; Williams et al., 1994), as well as sexual behaviour in non-monogamous rodents (Gil et al., 2011; Pedersen & Boccia, 2002). OT also plays a key role in non-sexual rodent social behaviour (Beery & Zucker, 2010; Lukas et

al., 2011), with OT antagonists inhibiting social preference formation in voles (Beery & Zucker, 2010). Relatedly, OT administration also leads to improved social recognition of conspecifics, whereas OT antagonists have been associated with impaired recognition (Ferguson et al., 2001; see Bielsky & Young, 2004 for a review), suggesting that OT plays a critical role in social memory (Ferguson et al., 2000; Lukas et al., 2013). In contrast, OT-deficient rodents show extensive social impairments, such as decreased maternal and sexual behaviours as well as reduced social interactions with their littermates (Francis et al., 2001; Pedersen & Boccia, 2002; Takayanagi et al., 2005). Importantly, the administration of exogenous OT appears to reverse these behavioural changes (Peñagarikano et al., 2015; Sala et al., 2011).

In humans, OT has also been shown to influence a number of social behaviours and cognitions. For instance, endogenous OT plays a central role in the development of healthy infant-mother attachment (Feldman et al., 2007; Galbally et al., 2011), perhaps by enhancing attachment security (Buchheim et al., 2009; Young et al., 2001). Recent studies have also suggested that OT plays a role in human parenting behaviours, much as it does in other mammalian species. Specifically, higher levels of endogenous OT are associated with increased attention towards and interactions with one's offspring in both male and female parents (see Feldman & Bakermans-Kranenburg, 2017 or Scatliffe et al., 2019 for reviews). The intranasal administration of OT also improves accurate emotion recognition (Marsh et al., 2010; Schulze et al., 2011) and facilitates positive communication behaviours during social conflict (Ditzen et al., 2009). Similar patterns of results have also been observed when contrasting different levels of endogenous OT (Gouin et al., 2010; Matsunaga et al., 2020). OT administration has also been shown to increase empathy towards another person's distress (Hurlemann et al., 2010; Shamay-Tsoory et al., 2013; Theodoridou et al., 2013). Relatedly, certain OT genetic polymorphisms have been associated with

increased trait empathy (Rodrigues et al., 2009; Wu et al., 2012). In contrast, lower levels of endogenous OT have been associated with a heightened risk for autism, a disorder which is characterized by pervasive socio-emotional deficits (Jacob et al., 2007; Lerer et al., 2008; Wu et al., 2005). Again, the administration of exogenous OT has been shown to ameliorate these social impairments, particularly in terms of the communication and identification of emotions (Andari et al., 2010; Hollander et al., 2007). Lastly, OT administration improves trust, generosity, and cooperation across a variety of social and economic games in which participants must work together to achieve a shared goal (Baumgartner et al., 2008; Kosfeld et al., 2005; Mikolajczak et al., 2010a; Mikolajczak et al., 2010b; Van IJzendoorn & Bakermans-Kranenburg, 2012; Zak et al., 2007).

Taken together, these findings have been interpreted to mean that OT is a prosocial hormone; that is, one that promotes helpful social behaviours and facilitates the cultivation of positive interpersonal relationships. In fact, this conception is so popular that OT is often referred to as the "love" or "cuddle" hormone in both the popular press (e.g.: Martin, 2015) and academic journals alike (e.g.: Colaianni et al., 2015). Relatedly, OT has been said to be a primary biological underpinning of the *tend-and-befriend* model (Taylor, 2006). According to this model, which is said to operate in parallel with the *fight-or-flight* system, one normative mammalian response to stress is to find conspecifics who can provide social support. In turn, this social support is believed to downregulate the physiological stress response and improve mood. OT is said to contribute to such behaviours in two ways. First, it facilitates the pursuit of social support by increasing social approach behaviours (Kemp et al., 2012; Yao et al., 2018) and dampening the neurobiological fear response (Ellenbogen et al., 2014; Kirsch et al., 2005; Koch et al., 2015). In support of this contention, OT administration has been found to selectively improve trust in individuals who

experience negative affect following a social stressor (Cardoso et al., 2013); a change that is likely to enable social support seeking behaviours. Second, it enhances the quality of such support by improving empathy and emotion recognition, as outlined above. However, others have argued that this universally prosocial perception of OT is perhaps a gross over-simplification considering more recent findings (e.g.: Yong, 2012).

Individual & Contextual Variability

Specifically, more contemporary research suggests that the effects of OT can be highly context dependent and that its well-publicized prosocial effects are less consistent than commonly recognized (see Bartz et al., 2011 or Shamay-Tsoory & Abu-Akel, 2016 for a reviews). In animal models, sex differences are the most prominent form of variability within the OT literature (see Caldwell et al., 2018 for a review). To illustrate, emerging evidence suggests that OT is only central to the sexual behaviour of female, but not male, rodents (Dhungel et al., 2019; Lazzari et al., 2013). Nonetheless, evidence of broader contextual variability also exists within the animal literature. For example, at least one study has found that OT does not unilaterally improve rodent social memory; instead, it selectively improves memory for potential sexual partners (Lukas et al., 2013).

Within human sample studies, even more robust evidence of variability has been reported. For instance, OT administration has been said to globally improve emotion recognition, as mentioned above (e.g.: Lischke et al., 2012a). In contrast, a growing body of literature suggests that this effect is largely driven by the improved recognition of angry and happy faces (Fischer-Shofty et al., 2010; Shin et al., 2018; see Shahrestani et al., 2013 for a meta-analysis); the recognition of other emotions (e.g.: sadness or disgust) is only minimally improved. Similarly, inter-individual factors have been found to mediate the relation between OT administration and

emotion recognition, such as sex (Bartz et al., 2019), age (Campbell et al., 2014), and psychopathology (Timmermann et al., 2017), amongst others. In fact, when included, sex is often found to mediate the effects of OT administration, sometimes producing completely opposite findings in men and women (e.g.: Boyle et al., 2022; Ebner et al., 2015; Lischke et al., 2012b; Zhu et al., 2019). Even within a relatively standardized procedure – such as monitoring eye gaze towards emotional faces – tremendous variability between studies has been observed. For example, a selection of studies on this topic have found that OT administration does not alter eye gaze (Lischke et al., 2012a), increases eye gaze to fearful, but not happy nor angry, faces (Le et al., 2020a), increases eye gaze to happy and fearful, but not neutral, faces (Tollenaar et al., 2013), or increases eye gaze towards neutral and happy, but not angry, faces (Domes et al., 2013). Variability has also been found in investigations of more complex social behaviours. To illustrate, OT has been found to selectively improve trust and generosity when interacting with a reliable, but not an unreliable, partner (Mikolajczak et al., 2010a). Further, interactions between contextual and individual factors have also been reported. For example, OT administration within a social context has been shown to increase perceived social support selectively in women, but not men, with more pronounced changes in those women who reported a greater motivation to socialize (Cardoso et al., 2016b). In contrast, when administered within a non-social context, OT produced a decrease in perceived social support, with larger effects in women who reported a greater motivation to socialize. In short, there is a substantial and growing body of literature showing that the effects of OT are highly variable, subject to both individual and contextual factors, as well as their countless permutations.

Effects on Autobiographical Memory

Despite this highly incongruent literature base, the evidence that OT does modulate a wide range of social behaviours and cognitions is compelling. Such broad changes likely reflect a confluence of underlying mechanisms, and some viable hypotheses have been proposed. For instance, OT may facilitate trust and social approach behaviours by downregulating the biological stress response (see Neumann, 2002 for a review) or attenuating amygdala reactivity (Domes et al., 2007). Nevertheless, OT's ability to heighten disparate behaviours under different contexts likely reflects additional underpinnings. One possibility is that OT's effects on social behaviour stem, at least in part, from its influence on autobiographical memory.

As mentioned above, OT has been shown to be critical in a rodents' capacity to form social memories that help maintain adaptive social recognition (e.g.: Ferguson et al., 2001). Interestingly, more recent works also suggests that OT plays an important role in the encoding and/or retrieval of information in humans as well. Much like in rodents, OT administration improves social recognition, as measured by the identification of previously seen faces (Rimmele et al., 2009; Savaskan et al., 2008). Another parallel between rodent and human models is that OT appears to selectively reinforce memory for socially relevant stimuli. Namely, memory is worsened for wordlists comprised of neutral (e.g.: cake) or somewhat ambiguous reproduction-related words (e.g.: pacifier) following OT administration (Heinrichs et al., 2004). In contrast, memory for wordlists made up of explicitly sexual (e.g.: kiss) or romantic (e.g.: love) words is improved following OT administration (Guastella et al., 2008; see Brambilla et al., 2016 for a review). Although this evidence does suggest that OT plays a role in human social and semantic memory, a different form of memory is likely even more important when attempting to predict behaviour.

Autobiographical memory (AM) – that is, memory for specific episodes from our past – is a potentially significant determinant of human behaviour. AMs play a meaningful role in our self-identity, and as such, in our interpretations of and interactions with the world around us (Conway, 2005). Previous works have already demonstrated that OT administration can alter patterns of AM recall. The first project to address this research question found that intranasal OT administration results in a more frequent recollection of positive social affiliation memories compared to placebo (Cardoso et al., 2014). This finding was interpreted as a key underpinning of OT's prosocial effects. That is, if OT facilitates the recall of positive social interactions, it might also lead to the expectation that future interactions will continue to be positive; in turn, this could produce social approach behaviours and prosocial tendencies.

However, subsequent work that has considered individual and contextual variability has undermined this straightforward interpretation. Specifically, it has been found that depressed participants recall a greater number of negative recollections following OT administration, but only in the absence of a socially supportive environment (Wong et al., 2021). As such, OT may instead increase the recall of autobiographical events that are congruent with existing biases and, in turn, promote behaviours that are consistent with those beliefs. In keeping with this suggestion, one study has found that greater recall of romantic-conflict memories following OT administration was predictive of subsequent relationship dissolution (Cardoso et al., 2016a); this suggests that OT can alter patterns of recollections according to implicit beliefs in ways that can be projected on to future behaviour.

Effects on Antisocial Behaviour

Given OT's common perception as a universally prosocial hormone, recent findings suggesting nuanced effects on trust and empathy are particularly salient. For instance, OT

administration has been shown to decrease, rather than increase, trust and cooperation when participants suffer from particular forms of psychopathology (Bartz et al., 2010a). Further, a series of studies by De Dreu and colleagues suggest that the nature of one's relationship with their interaction partner can be a particularly important in modulating the effects of OT (De Dreu at al., 2010; De Dreu et al., 2011; De Dreu et al., 2012; Zhang et al., 2019). Specifically, these studies found that if a confederate or participant can be framed as a competitor, exogenous OT increases antisocial behaviours such as hostility and competitiveness rather than improving trust or generosity. Parallel changes, such as reduced empathy towards individuals from different ethnic groups (Sheng et al., 2013) and reduced honesty towards individuals placed on arbitrary opposing teams (Shalvi & De Dreu, 2014), have also been reported following OT administration. In sum, OT appears to have vastly different effects on prosocial behaviour depending on the individual to whom and the context in which it is administered.

Findings such as these have been interpreted to mean that OT only enhances prosocial behavior towards one's in-group (e.g.: Sheng 2013), often at the expense of their out-group. Interestingly, a recurrent finding with the studies by De Drue and colleagues (2010; 2011; 2012) is in keeping with this proposition. Namely, they found that when antisocial behaviour would benefit only the participant, prosocial behaviours such as trust, generosity, and cooperation towards a competitor were unchanged by OT administration. In contrast, when antisocial behaviours stood to benefit the entire in-group, these prosocial tendencies were markedly reduced. One proposed model to explain these disparate findings is that OT increases prosocial behaviours when the social context is positive and perhaps ambiguous. However, when social cues indicate that the current environment is potentially threatening or competitive, OT instead enhances defensive antisocial behaviours (see Olff et al., 2013 for a review). The underlying assumption

being that out-group members are inherently seen as potential threats. In other words, OT might not be a universally prosocial hormone; rather, it appears to increase in-group solidarity at the expense of out-group solidarity, with potentially deleterious consequences (see Bethlehem et al., 2014 for a review). In the most extreme cases, these consequences could include overt aggression and physical violence.

Aggression & Violence

The relation between OT and aggression may be particularly relevant, as prior research has shown that as little as a single administration of exogenous hormones can modify patterns of aggression. Seminal work on the role of hormones in aggressive behaviour revealed that administering one dose of testosterone increases violence in rodents (e.g.: Beeman, 1947; Edwards, 1969). More recent work has found that the administration of exogenous testosterone also increases aggressive responding in humans (Pope et al., 2000; Wagels et al., 2018). The administration of other hormones, such as melatonin and progesterone, have also been found to increase violence and aggression in a variety of rodent species (Jasnow et al., 2002; Meisel & Sterner, 1990; Rendon et al., 2015). Interestingly, different results are obtained when using different rodent species or when additional hormone levels are manipulated (Kohlert & Meisel, 2001; Mayer et al., 1990). This yet again highlights the complex relationship between hormones and behaviour, with significant moderation by contextual and individual factors.

In keeping with this complex relationship, the association between aggression and other hormones, such as estrogen (see Trainor et al., 2006 for a review) and serotonin (see Duke et al., 2013 for a review), remains ambiguous despite extensive investigation. While many studies indicate that aggression has a positive relation with estrogen and a negative association with serotonin, incongruent findings suggestive of contextual (e.g.: Trainor et al., 2008) and individual

(e.g.: Kyomen et al., 1999) variability have been reported. Further, interactions between different hormonal systems are likely to complicate holistic biological models of aggression (e.g.: Halperin et al., 1997). In sum, while the association between hormones and aggression remains inadequately understood, emerging evidence suggests that OT may facilitate aggression under certain contexts.

Oxytocin & Animal Aggression

Animal research has found that disruptions of the OT system can result in changes to aggressive and proto-aggressive behaviours, such as pre-aggressive posturing and vocalization. Importantly, these findings have been replicated using a variety of methodologies that reliably reduce the biological availability of OT, such as eliminating OT synthesis (e.g.: Ragnauth et al., 2005; Winslow et al., 2000), the administration of OT antagonists (e.g.: Calcagnoli et al, 2013; Lubin et al., 2003), or reducing OT receptor density (e.g.: Hattori et al., 2015; Takayanagi et al., 2005). This is a particularly salient consideration, given that these different methodologies likely result in distinct developmental and neurological outcomes. That is, while the administration of an OT antagonist temporarily reduces the availability of OT in the brain, the offspring of OT knockout animals have never experienced the effects of OT, neither pre- nor post-partum (see Dhakar et al., 2012 for a more detailed review). This, in turn, can result in permanently altered neural networks. Further, because the mothers of these animals are OT knockouts themselves, they likely provided reduced care and nurturance (Francis et al., 2001), creating a confluence of atypical neural and social development. Although it is clear that disruptions to the OT system produce changes to aggressive behaviour, the exact nature and direction of these changes are not yet fully understood.

As with most findings in the OT literature, incongruent results between published studies are common. Nonetheless, a review of this animal literature does suggest a potential pattern of results. Specifically, when compared to genetically unmodified conspecifics, OT-knockout rodents

that have been deprived of OT from conception display elevated levels of aggression, whereas those whose OT systems are disrupted post-partum instead show decreased aggression. It would thus appear that prenatal exposure to OT is critical to the development of normative and adaptive patterns of aggression, whereas a postnatal lack of OT results in an overall dampening of aggressive behaviour. However, findings inconsistent with this proposed model have been published (e.g.: DeVries et al., 1997), and a complete understanding of the interplay between OT and aggression has not yet been achieved. Further, sex difference (e.g.: Bales & Carter, 2003) and inter-individual factors (e.g.: Bosch et al., 2005) complicate our understanding of the role of OT on aggression.

In studies measuring endogenous OT (Bosch et al., 2005) or administering exogenous OT (Ferris et al., 1992), it appears that elevated levels of OT can intensify physical violence when one's in-group is in danger; again, highlighting the importance of social context in the understanding OT's effects. More specifically, while higher levels of OT appear to reduce the incidence of spontaneous violence, they instead increase maternal violence when offspring are thought to be at risk. Interestingly, these findings could be integrated into the *tend-and-befriend* model under the stipulation that it is most evolutionarily adaptive to exclusively provide social support towards one's in-group and to exhibit aggression only towards one's out-group (Campbell, 2013). Under this updated model, OT would be predicted to increase the exclusion and marginalization of out-group members as a means of protecting and aiding one's in-group; a phenomenon known as parochial altruism (De Dreu et al., 2010). Likewise, a lack of endogenous OT could result in heightened aggression towards one's in-group, which has also been reported within the published literature (Hattori et al., 2015). Although, yet again, results incongruent with this proposition have been found (e.g.: Calcagnoli et al, 2013). While this suggested interpretation

may help conceptualize the role of OT in non-human animal aggression, the overall state of the literature still remains ambiguous. Moreover, the role of OT in human aggression is even less well understood.

Oxytocin & Human Aggression

There is tentative evidence that OT does play a meaningful role in human aggression. Firstly, several of the widely accepted behavioural and cognitive changes seen following OT administration are contrary to the behavioural patterns seen in individuals at a heightened risk of aggression and violence. For instance, OT improves emotion recognition, as outlined above; an ability which is otherwise impaired in individuals diagnosed with or at-risk for antisocial personality disorder and psychopathy (see Marsh & Blair, 2008 or Dawel et al., 2012 for reviews). Parallel findings have also been reported regarding empathy (see Megias et al., 2018 for a review) and eye gaze (e.g.: Dadds et al., 2006; Dadds et al., 2010), which are also impaired in such at-risk individuals. Particular OT genetic polymorphisms have been associated with increased callousness in children (Beitchman et al., 2012; Malik et al., 2012) and aggression in adolescents (Smearman et al., 2015), both of which are said to be predictive of later antisocial personality disorder. Similarly, low levels of endogenous OT have been found within individuals diagnosed with borderline personality disorder (Bertsch et al, 2013a; Carrasco et al., 2020), which – despite being characterized by self harm – can also result in heightened aggression and violence (see Sansone & Sansone, 2012 for a review). Taken together, these findings suggest that the OT system may be dysregulated in personality types and disorders that are predictive of violence and aggression in humans, a hypothesis that has also been argued elsewhere (Dadds et al., 2013a; Dhakar et al., 2012).

Secondly, although limited in number, studies directly investigating the relation between endogenous OT and aggressive behaviours in humans do suggest a likely association. For instance, biomarkers of endogenous OT have been both positively (Fetissov et al., 2006) and negatively (Lee et al., 2009) associated with aggressive behaviour in males. Similarly, endogenous OT levels have been found to be higher in a criminal sample when compared to non-incarcerated controls (Mitchell et al., 2013). In terms of exogenous OT, the previously summarized works of De Drue and colleagues have found a positive association between OT administration and competitive aggression; however, more recent works have both replicated (Ne'eman et al., 2016) and failed to replicate these findings (Zhu et al., 2019). Further, at least one study has investigated the effects of OT administration on aggressive behaviour in antisocial personality disorder without significant results (Alcorn et al., 2015). Importantly, the direction and magnitude of behavioral changes following OT administration was inconsistent between participants, again demonstrating the importance of inter-individual factors. Beyond reinforcing the importance of individual variability, such results also call into question whether the corrective behavioural effects of OT administration seen in OT-deficient rodents persist in human samples (e.g.: Sala et al., 2011; Sala et al., 2013), particularly among those at the greatest risk for violence. Although the underpinnings of these discrepant results are still unclear, it has been suggested that the interaction between OT, other hormones (namely, cortisol and testosterone), and early life adversity produce a unique risk profile for interpersonal aggression (see Fragkaki et al., 2018 for a review). As such, a more nuanced approach to OT research, with a particular emphasis on contextual and individual factors, will be necessary moving forwards.

Rationale & Goals of the Current Study

Based on this review of the literature, the present thesis aims to elucidate the role of OT as a determinant of aggressive behaviour using two distinct methodological approaches. First, we will conduct a meta-analysis of the animal literature investigating the relation between OT and aggression. We will specifically focus on gene-knockout studies, as these make up the bulk of published investigation and allow for direct control over OT's developmental availability. To control for inter-species variability in OT sensitivity, we will focus exclusively on investigations using mouse samples, which make up the majority of OT-knockout studies. We predict that, across studies, OT deficient mice will show increased aggression on several behavioural outcomes (i.e.: attack frequency, latency to first attack, total conflict duration) when compared to non-genetically modified conspecifics. We also predict that OT deficient mice will exhibit greater intrastrain aggression, as a consequence of a reduced in-group bias. Given the importance of contextual and individual factors, we will also investigate potential moderators. One moderator of interest will be the life stage in which the OT system is disrupted. That is, we will compare conditional gene knockouts – in which genes are deactivated post-partum – to traditional gene knockouts – which occur pre-partum. In doing so, we will be able to distinguish between the effects of a complete absence of OT from conception and of a more targeted disruption of OT after birth. We predict that traditional gene knockout mice, that experience OT deficiencies during fetal development, will show more pronounced aggression when compared to conditional post-partum knockout rats. Additional moderators of interest will include sex, the setting and nature of the aggression paradigm, as well as the relation of the interaction partner (i.e., same vs. different strains).

Second, we will investigate the potential link between AM, OT, and aggression using a placebo-controlled administration of the Autobiographical Memory Test (Williams & Broadbent,

1986). This task is a well-validated measure of cued autobiographical memory recall, with a long history of use both within and beyond the OT literature (e.g.: Brittlebank et al., 1993; Cardoso et al., 2014; Debeer et al., 2009; Wong et al., 2021). This task is of particular relevance, as it allows participants to freely recall any autobiographical event in response to a cue word, with only few restrictions. We will also have participants rate the valence of their self-generated AMs, to investigate the emotional nature of their recollections. We predict that high-aggression participants will recall a greater number of negative life events compared to their low-aggression counterparts. Given that the social context has been previously shown to modulate the effects of OT during autobiographical memory tasks (Cardoso et al., 2016b; Wong et al., 2021), we will also include conditions with and without social support. We predict more frequent negative recollections following OT administration in the non-social condition for high-aggression participants.

Chapter 2: Behavioural Aggression in Oxytocin Gene Knockout Mice: A Meta-Analysis

Abstract

Although best known as a facilitator of prosocial behaviours, the nonapeptide oxytocin (OT) has been found to instead increase competitive and aggressive behaviours in certain contexts. Importantly, these findings are equivocal and a comprehensive understanding of the association between OT and aggressive behaviours has not yet been achieved. To further elucidate this relation, we conducted a meta-analysis of studies investigating aggressive behaviour in mice following a genetic manipulation of the OT system. We found that OXTR knockout mice exhibited significantly heightened aggression in adulthood. In contrast, OXT and OXTR FB knockout procedures were not associated with statistically significant changes to aggressive behaviour. Our results indicate that prenatal OT deficiencies are consistently and reliably associated with heightened adulthood aggression. Additionally, we found that behavioural paradigms that evoke naturalistic territorial and competitive challenges were more reliably associated with elevated aggression following disruptions to the OT system, whereas social challenges produced inconsistent results. Lastly, we found that genetic manipulations of the OT system were associated with comparatively greater increases to intra-strain, relative to inter-strain, aggression. Together, these findings suggest that fetal OT availability is an important predictor of subsequent aggression, whereas post-natal OT deficiencies were not associated with changes to adulthood aggressive behaviour. They also indicate that OT is critical to the maintenance of normative in-group biases (the tendency to favor members of one's own group over members of other groups), at least in mice. Further, the relation between OT and aggression is influenced by additional contextual factors, in keeping with more contemporary models of OT's effects on human behaviour and cognition.

Introduction

The nonapeptide oxytocin (OT) has become widely recognized as a moderator of a large range of social behaviours and cognitions. In animals, procedures that increase the availability of OT have been found to improve social recognition (Popik & van Ree, 1991; Popik et al., 1992), whereas methodologies that reduce or eliminate the availability of OT lead to considerable impairments in this function (Ferguson et al., 2001; Oettl et al., 2016). Further, while the elimination of endogenous OT results in complete social amnesia, the subsequent administration of exogenous OT reverses this effect, producing normal social recognition (see Ferguson et al., 2002 for a review). Taken together, these findings suggest that OT is essential to foundational aspects of social functioning, such as social memory (Lukas et al., 2013). In turn, OT has also been found to play a critical role in more complex forms of social behaviour, such as intraspecies social affiliation. The OT system has been implicated in social preference formation in highly sociable species (Harrison et al., 2016; Landin et al., 2020), partner preference formation in monogamous species (Bales & Carter, 2003; Williams et al., 1994), and maternal behaviours across a variety of mammalian species (Keverne & Kendrick, 1992; Olazábal & Young, 2006; Rich et al., 2014). As with social recognition, impairments in more complex social functions subsequent to disruptions of the OT system are reversed following exogenous OT administration (e.g., Sala et al., 2011).

A growing body of evidence suggests that OT plays parallel roles in the social behaviours and cognitions of humans. For instance, a genetic polymorphism related to the synthesis of OT receptors has been associated with human social recognition skills (Skuse et al., 2013). Similarly, the administration of exogenous OT has been found to improve the recognition of previously seen faces without influencing memory for non-social cake (Rimmele et al., 2009). This suggests that, much like in non-human mammals, OT plays a central role in human social memory, perhaps as a

consequence of the high degree of OT receptor expression within the hippocampus (Lin & Hsu, 2018). Similarly, the OT system has been implicated in more complex human social behaviours. For instance, exogenous OT administration has been found to facilitate approach behaviours towards positive social stimuli (Cohen & Shamay-Tsoory, 2017; Preckel et al., 2014), which can be conceptualized as the first step in social affiliation. OT has also been found to play a potential role in human partner preference by mediating some of the cognitions and behaviours that could underlie monogamy. Specifically, exogenous OT administration has been found to increase the distance that romantically engaged, but not single, heterosexual males maintain between themselves and a novel female (Scheele et al., 2012). Likewise, OT administration leads men to rate their current romantic partners as more attractive, without producing parallel improvements in the ratings of other women (Scheele et al., 2013). Further, OT seems to influence human parenting behaviours, with higher levels of endogenous OT being associated with greater attention towards and more frequent interactions with one's offspring (see Scatliffe et al., 2019 for a review). OT has also been implicated in numerous higher order social behaviours that do not necessarily have clear animal-model analogues, such as trust (Mikolajczak et al., 2010a; Mikolajczak et al., 2010b), generosity (Zak et al., 2007), and healthy interpersonal communication (Ditzen et al., 2009). In sum, OT has been found to be a key component in a wide range of social behaviours in humans and animals alike.

A particularly salient and unwanted form of social behaviour is interpersonal aggression. Historically, OT has been assumed to impede aggression, given its strong empirical association with prosocial behaviours and the maintenance of healthy relationships (e.g., de Jong & Neumann, 2017). Under this model, procedures that would increase the availability of OT are expected to reduce aggression while those that would diminish the presence of OT should amplify aggressive

behaviour. However, recent works that have addressed this assumption have met with inconsistent results. Certainly, some animal studies have found that the administration of exogenous OT results in reduced aggression (Calcagnoli et al., 2013; Consiglio et al., 2005). Likewise, a parallel pattern of results – heightened aggression when the availability of OT is reduced – has also been reported across different methodological approaches. Both the administration of OT antagonists (Lubin et al., 2003) as well as genetic manipulations that limit the synthesis of endogenous OT (Ragnauth et al., 2005) have been associated with increased aggression in rodents. Nonetheless, incongruent findings, in which reductions to the availability of OT result in reduced aggression, have also been reported (DeVries et al., 1997, Winslow et al., 2000). Similar inconsistencies can also be found between studies using human participants, despite a much smaller literature base. For instance, one study found that endogenous levels of OT are negatively associated with self-reported lifetime aggression (Lee et al., 2009), keeping with the idea that OT impedes aggressive behaviour. In contrast, the administration of exogenous OT has been found to heighten levels of aggression and competitiveness across different economic games (De Drue et al., 2012; Ne'eman et al., 2016). While it is clear that the OT system plays a role in the emergence of aggressive behaviours, the exact nature of this relation remains clouded by incongruent findings.

One plausible hypothesis to explain the heterogeneous state of this literature is that the effects of OT are themselves highly heterogeneous. That is, a growing body of literature suggests that the effects of OT are subject to both individual and contextual factors which contribute to the considerable variability seen between some published results (e.g.: Bartz et al., 2011; Wong et al., 2021). To illustrate, OT administration has been found to selectively improve generosity in high-empathy participants (Strang et al., 2017), but to reduce generosity during an economic game in which participants had unilateral power (Radke & de Bruijn, 2012). OT administration has also

been shown to selectively increase trust towards reliable, but not unreliable, strangers (Mikolajczak et al., 2009) and to decrease trust in participants with a particular psychiatric disorder (Bartz et al., 2010a). These highly variable effects seem to persist within the aggression literature as well. For instance, men high in trait-anger show greater aggressive responding during a competitive economic game following OT administration, whereas low-anger men exhibit no such changes in aggressive behaviour (Alcorn et al., 2015). Similarly, another study found that the administration of intranasal OT resulted in a greater propensity towards (hypothetical) intimate partner violence selectively in high trait-aggression males (DeWall et al., 2014). These results suggest that exogenous OT may amplify underlying propensities towards violence in men with a greater baseline tendency for aggression. In women, anxiety, rather than anger, seems to be a key inter-individual factor. Research has found that OT administration reduces the aggressive responses of women throughout an economic game, but only for high state-anxiety participants; women low in anxiety demonstrated no behavioural changes under OT (Campbell & Hausmann, 2013). This suggests that exogenous OT inhibits aggression in anxious women, perhaps by selectively reducing amygdala activity as has been observed in a sample of highly anxious individuals (Labuschagne et la., 2010). Interestingly, female rats specifically bred to display high levels of anxiety show reduced maternal aggression following the administration of an OT antagonist (Bosch et al., 2005). In this case, reduced, rather than increased, levels of OT were selectively associated with decreased aggression in high-anxiety females. Although such direct contrasts between human and animal models are invariably limited, this pair of findings does nonetheless highlight the important interplay between individual and contextual factors that determines the effects of OT. Taken together, these findings illustrate a complex relationship

between OT and social behaviour; one that is heavily moderated by individual factors resulting in inconsistent, and sometimes diametrically opposed, effects.

Likewise, contextual differences between methodologies have also been found to alter the relation between OT and aggression. For instance, genetic manipulations that reduce the synthesis of the OT peptide have been found to decrease aggression between conspecifics in a shared, neutral environment (Lazzari et al., 2013), but to increase aggressive behaviour when faced with an intruder in one's home cage (Ragnauth et al., 2005). As above, these findings exemplify diametrically opposed OT effects under different conditions. However, incongruent results have also been reported between largely identical approaches (e.g., Pagani et al., 2015 vs. Takayanagi et al., 2005), suggesting yet again that the interplay between individual and contextual factors is key to adequately understanding the effect of OT on social behaviours. To date, investigations that have attempted to elucidate this interplay within the aggression literature have repeatedly identified one key phenomenon: a concept known as in-group bias or in-group favoritism. Defined as a tendency to favor members of one's own group over members of other groups, in-group bias is a well validated psychological concept that likely underlies our species' tribalistic past and often prejudiced present (see Everett et al., 2015 for a review).

In-group biases are particularly salient in a discussion of contextual factors given that they are an inherent reflection of the changing dynamics between the self and our environment. That is, our self-identified group membership can change over time, often as a function of our changing social environments (Tanti et al., 2011). Likewise, the ways in which we exhibit these in-group biases can also change over time, depending on the perceived status or stability of our in-groups (Scheepers et al., 2006). Critically, research has found that OT may play a very fundamental role in the nature of our in-group identities. Namely, one study that contrasted intra- vs interstrain social

recognition in OT deficient mice found that OT was essential to recognizing same-strain conspecifics, but that the recognition of different strain mice was not impaired in the absence of endogenous OT (Macbeth et al., 2009). This suggests that OT is crucial to identifying in-group members. In humans, OT administration reduces empathy towards individuals belonging to racial or ethnic groups different from our own (Sheng et al., 2013), perhaps reflecting a heightened sense of belonging and loyalty to our own in-groups. Relatedly, OT administration has been found to amplify aggression within competitive contexts, facilitating hostility towards one's opponents when such behaviours might benefit their randomly assigned team (De Dreu at al., 2010; De Dreu et al., 2011; De Dreu et al., 2012). Taken together, these findings have been interpreted to mean that OT increases parochial altruism; that is, altruistic or self-sacrificial behaviours that aim to exclusively assist one's in-group, often at the expense of the out-group. In other words, OT may operate in a highly selective fashion, facilitating prosocial behaviours such as trust and generosity towards one's in-group and simultaneously amplifying anti-social behaviours such as aggression and competitiveness towards one's out-group (see De Dreu, 2012 for a review).

One final consideration that may contribute to the seemingly inconsistent relationship between OT and aggression is the timeframe in which OT is manipulated. That is, OT manipulations may have different effects at different points across the lifespan. There is already evidence for this contention outside of the aggression literature. For instance, the acute administration of OT after sexual maturity facilitates partner preference formation in monogamous voles, as outlined above; in contrast, chronic exogenous OT administration prior to sexual maturity result in decreased partner preference once adulthood is reached (Bales et al., 2013). In humans, exogenous OT administration has been found to selectively improve emotion recognition in older adult men, but not for their young adult peers (Campbell et al., 2014). In both cases, these results

may reflect developmentally-dependant impact of OT, which are subject to the life stage of the individual and the corresponding level of neurological development. Similar propositions have already been made within the aggression literature, following a collection of studies that contrasted the aggressive behaviour of mice with genetically induced OT deficiency either pre- or postnatally (Takayanagi et al., 2005). It was found that, compared to wild type (WT) conspecifics, mice with no fetal or lifetime exposure to OT were more aggressive in adulthood; in contrast, mice with no postnatal exposure to OT were less aggressive than their WT peers. Taken together, these findings suggest that the timing of OT manipulations might be an important moderator of their effects.

In sum, while a relation between OT and aggressive behaviour has been supported by numerous animal- and human-model studies, the exact nature of this relationship remains poorly understood. This present study aims to elucidate our understanding by assessing the magnitude and direction of the relationship between OT functioning and aggression via a systematic meta-analysis of the animal literature. We will focus on animal-model genetic-knockout studies, for a combination of practical and theoretical reasons. Most plainly, this methodological approach represents the largest portion of research in this field and is thus best suited for a comprehensive evaluation of published results. For this same reason, as well as to control for intraspecies variability in OT function and sensitivity, we will exclusively investigate projects that used genetically altered mouse samples. From a theoretical perspective, genetic manipulations may be an especially viable approach to investigating the relation between OT and aggression, as they allow for targeted manipulations of OT availability at different points in an animal's lifespan (see Dhakar et al., 2012 for a review). In particular, three types of genetic manipulations have been included in the literature to date, each targeting a different genetic underpinning of the OT system. The oxytocin-neurophysin gene (OXT) is required to produce a protein precursor needed to

synthesize endogenous OT. The oxytocin receptor gene (OXTR) is required for the genesis of OT receptors throughout the brain. Lastly, the conditional oxytocin receptor forebrain knockout (OXTR FB) eliminates OT binding selectively in the forebrain in the weeks following birth. Critically, manipulations of these genes will produce unique patterns of developmental effects. That is, while the OXT gene knockout eliminates the ability to synthesize endogenous OT, prenatal exposure to maternal OT remains possible. In contrast, the OXTR gene knockout eliminates the expression of OT receptors throughout the whole brain; as such, these animals are never exposed to endogenous or exogenous OT at any point, even in utero. Lastly, the OXTR FB knockout specifically disrupt OT receptor functioning in the forebrain, starting at approximately 21 days of age. By contrasting these three genetic manipulations, we can better understand the differential effects of OT deprivation prenatally, postnatally, and throughout the entire lifespan. We will also contrast aggressive behaviour between same-strain and different strain mice, which will serve as a biologically based in-group. Additional considerations, such as sex and type of aggression paradigm will also be evaluated, to identify potential contextual factors. We predict that, across studies, OT deficient mice will show increased aggression in comparison to their WT conspecifics, but that this effect will be moderated by the nature of the genetic manipulation. Specifically, we anticipate that prenatal OT deficiency (OXTR knockouts) will be the strongest predictor of lifetime aggression, as has been suggested previously in the literature. We also anticipate that OT deficient mice will exhibit greater intrastrain aggression, as a consequence of a reduced in-group bias.

Method

Inclusion Criteria

A preliminary literature review was conducted to identify the most common species and polymorphisms within OT genetic research; these findings were used to guide our inclusion criteria

as to maximize the number of eligible articles while also maintaining a necessary degree of methodological and biological consistency between studies.

To be included in this meta-analysis, articles needed to meet the following inclusion criteria: (1) the sample was composed of mice; (2) the procedure included a genetic knockout that specifically targeted the OT system; (3) reported results included at least one measure of aggressive behaviour. Only English language articles were considered for this project. Studies of any sample size or sample strain were included in these analyses. Similarly, all types of OT genetic knockouts, behavioural paradigms, and aggression measures were eligible, as long as the above criteria were met. Only original research projects published in peer-reviewed journals were considered.

Search Strategy

The literature search was completed independently by two members of the research team, using the same search strategy and inclusion criteria. The search was completed in November 2021, and there were no restrictions in terms of publication date. The search was conducted on *PsycINFO* and *PubMed* (*MEDLINE*) using an identical approach. A backwards citation search was also completed using the first wave of eligible articles.

The specific search criteria used were: (1) Oxyt*; (2) aggres* OR viol*; (3) rodent OR mouse OR mice; (4) gene* OR knock* OR null* OR KO. This search strategy produced 180 results across both databases; of those results, 23 met the above-mentioned inclusion criteria. Twelve of these articles were removed: 11 were duplicates and one was a second publication using a previously published dataset. Of the 11 remaining articles, nine did not include the quantitative data required for a meta-analysis. These research teams were contacted, and the raw data was included in our analyses if available. If no longer available or if no response was received, raw data was estimated from graphs and figures by two independent research team members; any

discrepancies were resolved by consensus. One additional article was excluded as the authors did not respond to our request and there was not enough information in the figures to estimate quantitative outcomes. The final number of articles included in our analyses was ten, representing 21 unique experiments. The screening process is illustrated in Figure 1.

Study Variables

The following key variables were extracted for each experiment: (1) type of genetic modification; (2) genetic status of parent mice; (3) type of behavioural paradigm; (4) aggressive behaviour outcomes; (5) strain of interaction partner. Additional sample characteristics and methodological considerations (e.g.: sex, age, relation to interaction partner, etc.) were also collected. Means and standard deviations of aggression outcomes were obtained using the procedure outlined above. A list of all included publications and key extracted data are presented in Table 1.

Data Extraction and Coding

The same two members of the research team that completed the literature search also independently coded all study variables; any discrepancies were resolved by consensus. Most study variables were dummy coded, except for quantitative aggression outcomes which were estimated from figures to the first decimal point when raw data was unavailable.

Across all 21 experiments, the OXT gene knockout was the most common genetic manipulation (10 experiments; ~48% of included data), followed by the OXTR gene knockout (7 experiments; ~33%), with the OXTR FB knockout being the least common (4 experiments; ~19%). In terms of aggression measures, the most common behavioural outcome was frequency of attacks (bites, scratches, and pounces), which was reported in all studies (21 experiments; 100%). Additional measures, including latency to first attack (10 experiments; ~48%) and total duration

of the aggressive confrontation (11 experiments; ~52%), were less consistently reported. Across studies, the most common behavioural paradigms were as follow: (1) the resident-intruder procedure, in which a novel conspecific is introduced to the home-cage of an experimental animal; (2) the neutral-arena procedure, in which an experimental animal is placed in a large shared space with novel conspecifics; (3) the feeding-challenge procedure, in which multiple conspecifics are placed in a food-rich shared space, wherein the layout allows only a limited number of animals to feed at a time. In terms of their distribution, the resident-intruder task was by far the most common (14 experiments; ~66%), followed by the neutral-arena procedure (3 experiments; ~14%) and the feeding-challenge procedure (1 experiment; ~6%). Three experiments (~ 14%) used variations of these paradigms and were coded together as "other". In terms of parental genetic status, most studies used heterozygous mating (15 experiments; ~71%) whereas homozygous KO mating was uncommon (1 experiment; ~5%). The remaining experiments used mixed (~19%) or unspecified (~5%) mating procedures. In terms of strain of the interaction partner, the majority of publications used a partner of a different strain (16 experiments; ~76%) whereas a same strain partner was uncommon (2 experiments; ~10%). The remaining publications (3 experiments; ~14%) did not explicitly specify the strain of the interaction partner; while it is most likely that these procedures also used a different strain partner, they were nevertheless coded as "other" for the sake of accuracy.

Lastly, most studies (13 experiments; ~62%) contrasted two experimental groups (most commonly, knockout vs. WT) while the remaining procedures (8 experiments; ~38%) contrasted three groups (most commonly, homozygous knockout vs. heterozygous knockout vs. WT). Data from all experimental groups was included in our analyses.

Data Analysis

Global and subgroup effect sizes were computed using the *Meta-Analysis* procedure included in SPSS, contrasting mean differences in aggression outcomes between knockout and WT groups. Additional effect sizes were computed to contrast heterozygous and homozygous knockout groups when those data were available. The Hedges' g statistic was used in all analyses, as this effect size measure is the recommended approach when contrasting groups of different sample sizes (Card, 2016), which was the case for most of the projects included here. Given the heterogeneity of study designs, as well as the considerable empirical evidence for contextual effects in the OT literature, a random-effects model was used for all analyses; this is the recommended statistical approach when effects are predicted to differ between studies (Higgins et al, 2019).

Three of the 21 included experiments did not report standard deviations for subsets of their data due to extreme aggression scores. Specifically, only a single knockout mouse displayed aggressive behaviour in two experiments, whereas all knockout female mice in the third experiment were maximally infanticidal. In all three cases, there was an absence of variation in aggressive behaviour meaning that standard deviations could not be computed. These three experiments were excluded from the respective meta-analyses contrasting outcomes for which they had no variability data. They were nonetheless retained for this project to be evaluated qualitatively. A list of computed effect sizes for each included experiment is presented in Table 2.

Additionally, Egger's Regression Test was used to investigate possible publication bias within this literature and Cochran's Q statistic was used to investigate inter-study heterogeneity. All analyses were run using SPSS version 28 (IBM Software, Armonk, NY).

Results

Risk of Bias

Publication bias for attack frequency outcomes was assessed using Egger's Regression Test, which revealed significant asymmetry in published results ($Z = -3.030$, $p < 0.001$). A visual inspection of the funnel plot suggested that this discrepancy was largely driven by a single publication (Ragnauth et al., 2005), which found atypically large increases in aggressive behaviour following disruptions to the OT system. While it is unclear why this project produced such extreme group differences, it is plausible that their pattern of findings reflects unique aspects of their sample; specifically, this was one of only two publications to use a female sample. One recommended approach to identify outliers within a meta-analysis that may unduly skew aggregate findings is to contrast effect size confidence intervals (Harrer et al., 2021). Specifically, studies whose lower limit 95% confidence interval is greater than the upper limit of the pooled 95% confidence interval are said to be outliers with extreme large effects. This was true of both experiments published by Ragnauth and colleagues that included variance data (2005), but not any of the other included publications. Given that the inclusion of such extreme scores could undermine the validity and generalizability of our aggregate findings, this study was removed from all subsequent analyses; a practice that has been used in prior meta-analyses (e.g.: Blanck et al., 2018; Ford et al., 2019). Once removed, Egger's Regression Test was no longer significant ($Z = -3.886$, $p = 0.122$) and the funnel plot showed a more reasonable distribution of effect sizes (see Figure 2).

Parallel analyses revealed no significant asymmetry amongst studies that included outcomes of attack latency ($Z = 5.810$, $p = 0.163$) or conflict duration ($Z = -6.261$, $p = 0.109$). Funnel plots for attack latency and duration are included in Figures 3 and 4, respectively.

Global Effects

Across all included studies, OT knockout mice exhibited no significant differences compared to WT mice, across all aggression outcomes. Although the most pronounced effect was observed in terms of attack frequency, with OT knockout mice being more aggressive, this finding did not reach the conventional level of statistical significance (Z = 1.930, SE = 0.217 p = 0.054, Hedges' g = 0.419, 95% CI [-0.007, 0.846]). There were no significant group differences between OT knockout mice and WT mice in terms of latency to first attack (Z = -0.914, SE = 0.294, p = 0.361, Hedges' g = -0.268, 95% CI [-0.844, 0.307]) or total duration of aggressive behaviour (Z = 0.050, SE = 0.304, p = 0.960, Hedges' g = 0.015, 95% CI [-0.581, 0.612]). Additionally, significant heterogeneity was found between studies in terms of attack frequency (Q = 50.06, p < 0.01, I^2 = 71%), latency (Q = 27.05, p < 0.01, I^2 = 71%), and duration (Q = 28.91, p < 0.01, I^2 = 73%).

Given this heterogeneity, as well as the previously mentioned evidence of contextual and individual variability in the effect of OT on social behaviour, additional subgroup analyses were completed. The pattern of findings is discussed in the sections below; results of the statistical analyses for measures of attack frequency, attack latency, and attack duration are included in Tables 3, 4, and 5, respectively. Forest plots illustrating the distribution of effect size across studies for measures of attack frequency, attack latency, and attack duration are included in Figures 5, 6, and 7, respectively.

Effects of Genetic Manipulation

OXT knockout mice demonstrated no significant group differences in terms of attack frequency (p = 0.633, Hedges' g = 0.195), latency (p = 0.804, Hedges' g = 0.082), or duration (p = 0.602, Hedges' g = -0.219) when compared to WT mice. In contrast, OXTR knockout mice were significantly more aggressive than WT mice, exhibiting a greater frequency of attacks (p < 0.001,

Hedges' $g = 0.849$), a shorter latency to first attack ($p < 0.001$, Hedges' $g = -1.516$), and a longer total duration of aggressive behaviour ($p = 0.001$, Hedges' $g = 1.082$). Lastly, OXTR FB knockout mice demonstrated no significant group differences in terms of attack frequency ($p = 0.386$, Hedges' $g = -0.296$), latency ($p = 0.846$, Hedges' $g = 0.065$), or duration ($p = 0.165$, Hedges' $g = -0.474$) compared to WT mice.

Effects of Behavioural Paradigm

Under the resident-intruder paradigm, OT knockout mice exhibited no significant differences compared to WT mice, across all aggression outcomes. Although the most pronounced effect was observed in terms of attack frequency, with OT knockout mice being more aggressive, this finding did not reach the conventional level of statistical significance ($p = 0.073$, Hedges' $g = 0.460$). There were no significant group differences between OT knockout mice and WT mice in terms of latency to first attack ($p = 0.123$, Hedges' $g = -0.484$) or total duration of aggressive behaviour ($p = 0.525$, Hedges' $g = 0.228$).

Under the neutral-arena paradigm, there were no significant group differences between OT knockout mice and WT mice in terms of attack frequency ($p = 0.243$, Hedges' $g = 0.627$), latency ($p = 0.801$, Hedges' $g = -0.111$), or duration ($p = 0.176$, Hedges' $g = -0.608$).

Across the two experiments that used miscellaneous paradigms, there were no significant group differences between OT knockout mice and WT mice in terms of attack frequency ($p = 0.890$, Hedges' $g = -0.129$). Only one of these experiments reported additional aggression outcomes, finding that OT knockout mice exhibited a significantly longer latency to first attack ($p = 0.022$, Hedges' $g = 1.088$), without any significant group differences in conflict duration ($p = 0.082$, Hedges' $g = -0.802$).

The one experiment that used the feeding-challenge paradigm was excluded from these analyses (Ragnauth et al., 2005), but reported extreme increases in attack frequency.

Effects of Parental Mutation

Across all experiments that used the offspring of heterozygous pairings, there were no significant group differences between OT knockout mice and WT mice in terms of attack frequency (p = 0.286, Hedges' g = 0.294), latency to first attack (p = 0.576, Hedges' g = -0.239), or total duration of aggressive behaviour (p = 0.998, Hedges' g = 0.001).

For the offspring of mixed parings, no significant group differences between OT knockout mice and wild type mice were observed in terms of attack frequency (p = 0.413, Hedges' g = 0.455) or latency (p = 0.975, Hedges' g = 0.010). In contrast, such OT knockout mice exhibited significantly shorter durations of conflict than WT mice (p = 0.042, Hedges' g = -0.646).

Only one experiment used the offspring homozygous knockout pairings, finding that OT knockout mice were significantly more aggressive than WT mice, exhibiting a greater frequency of attacks (p = 0.023, Hedges' g = 1.201), shorter latency to first attack (p = 0.036, Hedges' g = -1.097), and longer total duration of aggressive behaviour (p = 0.004, Hedges' g = 1.613).

Only one experiment used the offspring of unspecified pairings, finding that OT knockout mice were more aggressive than WT mice in terms of attack frequency, although this effect did not reach the conventional level of statistical significance (p = 0.053, Hedges' g = 0.868). No other aggression outcomes were reported in this project.

Effects of Intruder Strain

Across all experiments that used a different-strain interaction partner, OT knockout mice were significantly more aggressive than WT mice, exhibiting a greater frequency of attacks (p = 0.029, Hedges' g = 0.468). However, there were no significant group differences in terms of

latency to first attack (p = 0.114, Hedges' g = -0.431) or total duration of conflict (p = 0.714, Hedges' g = 0.120).

With the exclusion of the study by Ragnauth and colleagues (2005), only one experiment used same-strain interaction partners. They found that OT knockout mice were significantly more aggressive than WT mice, exhibiting a greater frequency of attacks (p = 0.017, Hedges' g = 1.234). No other aggression outcomes were reported in these projects.

With the exclusion of the study by Ragnauth and colleagues (2005), only one experiment used an unspecified interaction partner strain. They found that OT knockout mice were significantly less aggressive than WT mice, demonstrating reduced attack frequency (p = 0.023, Hedges' g = -1.080) and longer latency to first attack (p = 0.022, Hedges' g = 1.088). They also exhibited a shorter duration of aggressive behaviours, although this finding did not reach the conventional level of statistical significance (p = 0.082, Hedges' g = -0.802).

Effects of Sex

Across all experiments, there were no significant group differences between male OT knockout mice and male WT mice. Although the most pronounced effect was observed in terms of attack frequency, with male OT knockout mice being more aggressive, this finding did not reach the conventional level of statistical significance (p = 0.055, Hedges' g = 0.443). There were no significant group differences between male OT knockout mice and male WT mice in terms of latency to first attack (p = 0.337, Hedges' g = -0.315) or total duration of aggressive behaviour (p = 0.841, Hedges' g = 0.068).

With the exclusion of the study by Ragnauth and colleagues (2005), only one experiment used a female sample. They found no significant group differences between female OT knockout

mice and female WT mice in terms of attack frequency (p = 0.888, Hedges' g = 0.073), attack latency (p = 0.833, Hedges' g = 0.109) or conflict duration (p = 0.430, Hedges' g = -0.412).

Contrast with Heterozygous Mutations

Across the eight experiments that included heterozygous OT knockout mice, there were no significant group differences between heterozygous knockout mice and WT mice in terms of attack frequency (Z = -1.031, p = 0.302, Hedges' g = -0.167, 95% CI [-0.484, 0.150]), latency to first attack (Z = 0.057, p = 0.955, Hedges' g = 0.014, 95% CI [-0.457, 0.484]), or total duration of conflict (Z = -1.220, p = 0.223, Hedges' g = -0.292, 95% CI [-0.762, 0.177]).

Similarly, there were no significant group differences between heterozygous knockout mice and homozygous knockout mice in terms of attack frequency (Z = 1.263, p = 0.207, Hedges' g = 0.428, 95% CI [-0.236, 1.092]), latency (Z = 0.265, p = 0.791, Hedges' g = 0.071, 95% CI [-0.451, 0.592]), or duration (Z = -0.988, p = 0.323, Hedges' g = -0.366, 95% CI [-1.091, 0.360]), across these eight experiments.

Additional analyses were used to contrast attack frequency between heterozygous and homozygous knockout mice, according to type of genetic manipulation. No significant group differences were found across the two OXT knockout experiments (Z = -1.204, p = 0.228, Hedges' g = -0.444, 95% CI [-1.168, 0.279]), or the two OXTR FB knockout experiments (Z = 0.432, p = 0.666, Hedges' g = 0.248, 95% CI [-0.878, 1.375]). Across the four OXTR knockout experiments that included heterozygous knockout mice, homozygous knockouts were significantly more aggressive (Z = 2.336, p = 0.019, Hedges' g = 0.925, 95% CI [0.149, 1.700]).

Additional Analyses

Follow-up analyses were completed using OXTR gene knockout experiments exclusively, as our findings revealed that this genetic manipulation produced the largest and most reliable

changes to aggressive behaviour. This specific manipulation consistently resulted in a greater frequency of aggressive behaviours, when compared to WT mice, across behavioural paradigms – resident intruder ($Z = 3.008$, $p = 0.003$, Hedges' $g = 0.728$, 95% CI [0.253, 1.202]), neutral arena ($Z = 3.481$, $p < 0.001$, Hedges' $g = 1.132$, 95% CI [0.495, 1.770]) – and interaction partner strain – same strain ($Z = 2.392$, $p = 0.017$, Hedges' $g = 1.234$, 95% CI [0.223, 2.244]), different strain ($Z = 3.738$, $p < 0.001$, Hedges' $g = 0.795$, 95% CI [0.378, 1.212]). In terms of parental mutation, OXTR knockout mice exhibited a greater frequency of attacks than WT mice when the offspring of heterozygous pairings ($Z = 3.675$, $p < 0.001$, Hedges' $g = 0.847$, 95% CI [0.395, 1.299]); a similar effect was observed for the offspring of unspecified pairings ($Z = 1.938$, $p = 0.053$, Hedges' $g = 0.868$, 95% CI [-0.010, 1.746]), although this did not reach the conventional level of statistical significance.

Parallel analyses (not reported here) were completed with OXT knockout experiments exclusively, revealing only two statistically significant differences in attack frequency. Namely, OXT knockout mice exhibited greater aggression than WT mice in the one experiment using the offspring of homozygous pairings (reported above). In contrast, they exhibited significantly reduced aggression in the one experiment using an unspecified interaction partner strain (also reported above). No significant group differences were observed across any remaining behavioural paradigms, parental mutations, or interaction-partner strains.

Parallel analyses (not reported here) were also completed with OXTR FB knockout experiments exclusively, revealing no significant group differences when compared to WT mice across all behavioural paradigms, parental mutations, and interaction-partner strains.

Discussion

The primary finding of the meta-analysis is that targeted genetic disruptions of the OT system that result in reduced OT availability are not consistently associated to changes in aggressive behaviour. Rather, our results indicate that these effects vary across different types of genetic manipulations and methodologies, suggesting that the relation between OT and aggressive behaviour is nuanced and heavily influenced by contextual and developmental factors. Two specific considerations are especially theoretically salient in our interpretation of the relation between OT and aggressive behaviours.

First, there were divergent findings across different types of genetic manipulations. We find the most robust and consistent effects of OT on aggressive behavior following procedures that disrupt the genesis of OT receptors throughout the whole brain from conception onwards (OXTR knockouts). Critically, these mice demonstrate increased aggression for all behavioural outcomes and across almost all methodological approaches. That is, this genetic manipulation seems to be the least susceptible to contextual factors, instead increasing aggression in most contexts with noteworthy consistency. In contrast, procedures that deactivate OT receptors primarily in the forebrain in the weeks after birth (OXTR FB knockouts) collectively produce no changes in aggressive behaviour, although a statistically non-significant trend towards decreased aggression was observed. Taken together, these findings suggest that prenatal reductions to OT availability amplify aggressive behaviour in adulthood, whereas postnatal reductions to OT availability instead minimize aggression, albeit less consistently. Although it is possible that the selective preservation of OT receptors in mid and hindbrain structures is contributing to this discrepancy, such an interpretation seems unlikely; an argument that has also been made elsewhere (Dhakar et al., 2012). Under the OXTR FB knockout procedure, OT receptors are preserved in the brain stem,

cerebellum, and midbrain. While these structures are critical to motor control, sensory perception and integration, and sensory-motor integration, they do not play a central role in motivated behaviours, such as territorial or parental aggression. More importantly, both OXTR and OXTR FB knockout mice show intact motor and perceptual functioning (Lee et al., 2008), suggesting that the availability of OT in non-forebrain regions does not differentiate these manipulations. Likewise, both OXTR and OXTR FB knockout mice show parallel deficits in same-strain social recognition (Macbeth et al., 2009), suggesting that differences in recognition are not contributing to this discrepancy. Rather, the key difference between OXTR and OXTR FB knockouts is the timing of receptor inactivation, with prenatal OT deficiencies being consistently associated with heightened aggression.

The third type of genetic manipulation, which instead disrupts the production of the OT peptide from conception but does not interfere with fetal exposure to OT (OXT knockouts), produced the most inconsistent results. Nevertheless, this approach did reveal some notable findings that merit further consideration. Most critically is the mating strategy used in the breeding of knockout mice. While mating procedures may influence offspring animals in several different ways, contrasting different mating techniques again allows us to examine the role of prenatal exposure. That is, while knockout animals that are unable to produce endogenous OT will have no exposure to the peptide postnatally, they may still be exposed to maternal OT in utero. In homozygous mating, however, the dame necessarily shares the same genetic knockout and, as such, has no endogenous OT of her own to convey to the fetus. The potential impact of this developmental difference is best highlighted in the work of Takayanagi and colleagues (2005). They found that, under otherwise identical experimental procedures, OXT knockouts from homozygous pairings were significantly more aggressive than their WT peers, while a similar

effect was not observed for heterozygous pairing knockouts. They suggest that the in-utero absence of OT is what underlies the discrepant levels of aggression seen in their two experiments. This is in keeping with our observed discrepancy between the behavioural outcomes of OXTR and OXTR FB knockout mice. That is, OXTR knockout mice – which demonstrate the most consistently elevated levels of aggression – also have no prenatal exposure to OT, as they lack the appropriate receptor sites for the peptide to bind to. In contrast, selective OXTR FB knockout mice – that do maintain a degree of prenatal OT exposure – have not been found to exhibit heightened aggression in any published studies to date. This pattern is further illustrated in Table 6.

One alternative interpretation for this pattern of results is that elevated aggression emerges from reduced maternal behaviours. Previous studies have found that OT knockout dames show diminished maternal behaviours, reflected by elevated pup abandonment and reduced maternal grooming (Rich et al., 2014; Pendersen et al., 2006). Such disruptions to normal early-life experiences may produce long-term changes to behaviour. Nonetheless, some studies have reported largely normal maternal behaviours in OT knockout dames across multiple genetic manipulations (Macbeth et al., 2010), including the aforementioned study by Takayanagi and colleagues (2005) which found elevated aggression in the offspring of homozygous pairings despite normal maternal behaviours. Unfortunately, studies using homozygous pairings are infrequent and our understanding of the effects of OT on fetal development are largely limited to procedures disrupting receptor genesis. Despite this limitation, our findings support and expand on the fetal developmental hypothesis. That is, mice whose parental pairings or genetic manipulations guarantee an absence of OT during fetal development consistently show elevated aggressive behaviours, even when maternal behaviours remain intact. Conversely, alternative procedures that only reduce the availability of OT postnatally show a trend towards reduced

aggression. Future research specifically contrasting the behavioural outcomes of homozygous versus heterozygous mating offspring is needed to fully elucidate this effect, but the present meta-analytic findings are consistent with the view that prenatal exposure to OT is a critical factor in adulthood aggression.

The second consideration of significant theoretical importance is the strain of the intruder/interaction partner. Our results indicate that, globally, OT knockout mice exhibited a trend towards greater aggression to novel mice both of their own strain as well as those belonging to a different strain, when compared to WT peers. However, we note a much larger effect size for intrastrain aggression, at least in terms of attack frequency. Previous research has found that WT mice exhibit greater aggression towards mice of a different strain compared to mice of their own strain (Hattori et al., 2015). As such, even reports of equivalent aggression towards same- and different-strain interaction partners would suggest a meaningful increase in intrastrain aggression. Increased intrastrain aggression following disruptions of the OT system is in keeping with more recent human research literature that suggests that OT heightens preferential in-group biases (e.g.: De Dreu et al., 2012; Zhang et al., 2019). In the absence of endogenous OT, this bias appears to become reduced or eliminated, resulting in heightened aggression regardless of strain. This may also account for the extreme levels of infanticide seen in OXT knockout mice (Ragnauth et al., 2005).

Additionally, we found that aggressive behaviour outcomes vary according to the behavioural paradigm used. Specifically, we find that the resident-intruder paradigm – in which a novel same-species intruder is introduced into the experimental animals' home cage – is the only technique to be consistently associated with markers of heightened aggression (i.e., increased attack frequency and duration, as well as shorter latency to first attack), although these findings

did not meet the conventional level of statistical significance. In contrast, the neutral-arena paradigm – in which a control animal and an experimental animal are both introduced to a novel shared space – produced less consistent results across studies. Although the reasons underlying this discrepancy remain unclear, one possible interpretation is that resident-intruder paradigms may be more effective in eliciting aggressive behaviour. That is, the inherently territorial nature of an intrusion into the home cage by a potentially harmful stranger, rather than encountering that stranger outside of the home, may be most effective in eliciting an aggressive response; a hypothesis which has also been suggested elsewhere (Takayanagi et al., 2005). A similar interpretation may also be relevant regarding the feeding-challenge paradigm, which might better elicit aggression given the inherently competitive nature of food scarcity. This could explain why this paradigm, used only once, elicited such a large effect size as to be classified as a statistical outlier. Lastly, the one study that used the free roam social exploration paradigm reported statistically significant decreases in aggressive behaviour. In this paradigm, which is analogous to the neutral-arena paradigm, animals are introduced into a shared social space that includes clear subdivisions, allowing for both social engagement as well as social avoidance. Of note, OT knockout mice in this study also displayed significantly fewer social behaviours (Lazzari et al., 2013), suggesting that the absence of OT resulted in reduced social approach. As such, it seems likely that the reduced aggression observed in that project was a product of the increased social self-isolation of knockout mice. In short, methodologies that reflect a competitive or territorial challenge may better elicit aggressive behaviours from OT deficient mice than paradigms that reflect a social challenge. However, it is also important to note that the type of genetic manipulation remains of primary importance, as it is only the OXTR knockout mice that were consistently more aggressive under these – and all other – behavioural paradigms.

One important shortcoming of this meta-analysis is the uneven distribution of genetic manipulations and experimental designs. Consequently, it is impossible to ascribe with absolute certainty the degree of influence of our proposed moderators. More plainly, it is difficult to assess the relative impact of intruder strain, mating strategies, and behavioural paradigms when such a large proportion of studies use the same procedures. Consequently, some of our subgroup contrasts may have lacked sufficient statistical power to accurately detect group differences. This is an especially salient consideration within the context of potential sex differences. The vast majority of projects included in this meta-analysis used exclusively male samples; as such, the generalizability of our findings to female mice is limited. Additionally, our exclusive focus on genetic knockout studies represents only a subset of investigations examining the link between OT and aggression. Although this approach is well suited to addressing developmental questions regarding OT exposure, we cannot comment on the relation between exogenous OT administration and aggressive behaviour. A complimentary quantitative review of in-vivo behavioural changes using agonist and antagonist studies would be an important next step in further clarifying the relation between OT and aggression. Relatedly, while our findings do further clarify the role of OT in mouse aggression, direct parallels to other animal species or to human models may be limited. Although the OT system is relatively conserved across mammalian species, human aggression is multifaceted and clearly influenced by complex environmental and socio-cognitive factors that are not necessarily reflected in animal behaviour. Further, our meta-analysis did not include a measure of study quality. Importantly, this was omitted as all studies included in our analyses were of comparable quality. They all used well validated approaches to producing and confirming the genotypes of experimental and control animals, as well as widely accepted behavioural paradigms and standardized methods of animal housing. Although guidelines for

evaluating the quality of animal-model medical research do exist (e.g: Hooijmans et al., 2010), the additional considerations they recommend (e.g.: home-cage humidity, type of food pellet) were uniformly missing from our included studies; it is also unclear how relevant these considerations are for behavioural, rather than medical, outcomes. As such, all included studies were considered to be of high quality. Lastly, certain valid studies were excluded from our analyses due to extreme levels of aggression, both high and low. Although the pattern of these extreme cases is largely in keeping with our overall findings (i.e., both extreme low-aggression scores were found in OXTR FB knockouts), it is possible that our analyses underestimate the degree of sex differences in the literature, as most female-sample studies were excluded.

In sum, disruptions to the OT system do play a critical role in subsequent aggressive behaviours, but this effect is profoundly modulated by additional factors. The most critical of these is the nature of the genetic knockout. Genetic manipulations that eliminate prenatal OT exposure (OXTR knockouts and homozygous OXT knockouts) result in increased aggression with notable reliability. In contrast, postnatal reductions in OT availability seem to decrease aggression, albeit less consistently. This suggests a paramount role of in-utero OT in the development of normative aggressive behaviours. Additionally, our findings suggest that OT plays a central role in the maintenance of normative in-group biases. Interestingly, intrastrain aggression was amplified following both pre- and postnatal disruptions to the OT system. Taken together, these findings suggest heightened global aggression following in-utero OT deprivation, but primarily elevated in-group aggression following postnatal OT deprivation. This hypothesis could be further developed by future studies that specifically contrast the behaviours of homozygous versus heterozygous pairing offspring (e.g.: Takayanagi et al., 2005), and that specifically contrast behaviour towards same- or different-strain conspecifics (e.g.: Hattori et al., 2015). These

experimental procedures, run across different type of OT genetic manipulations, would provide much needed clarity to this topic and strengthen the interpretations provided here. Ultimately, complex behaviours such as aggression likely reflect an interplay between both polygenic influences and contextual factors. In fact, these diverse underpinnings may explain some degree of the variability seen in published results. Nonetheless, the meta-analysis provides compelling evidence that OT is one such factor that contributes to aggressive behaviours and provides guidance for future research in this area.

Table 1. Summary of Extracted Data

Authors	Year	Number of experiments	Sample Size	Sex (% male)	Age range (in days)	Contrast	Parental Mutation	Paradigm	Strain
DeVries et al.	1997	2	30	100	122 - 183				
			30	100	122 - 183	OXT -/- vs. OXT -/+ vs. WT	Mixed	Resident Intruder	Different
			30	100	122 - 183	OXT -/- vs. OXT -/+ vs. WT	Mixed	Neutral Arena	Different
Dhakar et al.	2012	2	39	100	91 - 183				
			20	100	91 - 183	OXTR -/- vs. OXTR +/+	Heterozygous	Resident Intruder	Different
			19	100	91 - 183	OXTR FB -/- vs. OXTR +/+	Heterozygous	Resident Intruder	Different
Hattori et al.	2015	3	84	100	70 - 77				
			28	100	70 - 77	OXTR -/- vs. OXTR -/+ vs. WT	Heterozygous	Resident Intruder	Different
			28	100	70 - 77	OXTR -/- vs. OXTR -/+ vs. WT	Heterozygous	Resident Intruder	Different
			28	100	70 - 77	OXTR -/- vs. OXTR -/+ vs. WT	Heterozygous	Resident Intruder	Same
Lazzari et al.	2013	1	19	100	91 - 183	OXT -/- vs. WT	Heterozygous	FRSE	Unspecified
Pagani et al.	2015	3	58	70	70 - 212				
			22	100	70 - 135	OXTR FB -/- vs. WT	Heterozygous	Resident Intruder	Different
			19	100	89 - 212	OXTR FB -/- vs. OXTR +/- vs. WT	Heterozygous	Resident Intruder	Different
			17	0	80 - 120	OXTR FB -/- vs. OXTR +/- vs. WT	Heterozygous	Resident Intruder	Different
Ragnauth et al.	2005	3	36	0	56 - 81				
			12	0	56	OXT -/- vs. WT	Heterozygous	Feeding Challenge	Unspecified
			12	0	70 - 81	OXT -/- vs. WT	Heterozygous	Resident Intruder	Unspecified
			12	0	56	OXT -/- vs. WT	Heterozygous	Infanticide	Same
Sala et al.	2011	1	20	100	84 - 112	OXTR -/- vs. OXTR +/+	Unspecified	Neutral Arena	Different
Sala et al.	2013	1	29	100	84 - 112	OXTR -/- vs. OXTR -/+ vs. OXTR +/+	Heterozygous	Neutral Arena	Different
Takayanagi et al.	2005	3	53	100	98				
			18	100	98	OXTR -/- vs. OXTR +/+	Heterozygous	Resident Intruder	Different
			20	100	98	OXT -/- vs. OXT +/+	Heterozygous	Resident Intruder	Different
			15	100	98	OXT -/- vs. OXT +/+	Homozygous	Resident Intruder	Different
Winslow et al.	2000	2	43	100	> 50				
			27	100	> 50	OXT -/- vs. WT	Mixed	IIA	Different
			16	100	> 50	OXT -/- vs. WT	Mixed	Resident Intruder	Different

Note. OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene, +/+ = no genetic knockout, +/- = heterozygous genetic knockout, -/- = homozygous genetic knockout, WT = wild type, Strain = strain of interaction partner/intruder, FRSE = Free roam social exploration, IIA = Isolation induced aggression.

Table 2. Computed Effect Sizes

Authors	Year	Number of experiments	Sample Size	Sex (% male)	Contrast	Paradigm	Frequency	Latency	Duration
DeVries et al.	1997	2	30	100					
			30	100	OXT -/- vs. OXT -/+ vs. WT	Resident Intruder	-0.460	0.136	-0.717 *
			30	100	OXT -/- vs. OXT -/+ vs. WT	Neutral Arena	-0.406	0.116	-0.640 *
Dhakar et al.	2012	2	39	100					
			20	100	OXTR -/- vs. OXTR +/+	Resident Intruder	1.069 *	-1.750 *	1.208 *
			19	100	OXTR FB -/- vs. OXTR +/+	Resident Intruder	-0.604	0.035	-0.545
Hattori et al.	2015	3	84	100					
			28	100	OXTR -/- vs. OXTR -/+ vs. WT	Resident Intruder	0.159	-	-
			28	100	OXTR -/- vs. OXTR -/+ vs. WT	Resident Intruder	0.156	-	-
			28	100	OXTR -/- vs. OXTR -/+ vs. WT	Resident Intruder	1.234 *	-	-
Lazzari et al.	2013	1	19	100	OXT -/- vs. WT	FRSE	-1.080 *	1.088	-0.802 *
Pagani et al.	2015	3	58	70					
			22	100	OXTR FB -/- vs. WT	Resident Intruder	EN *	-	EN *
			19	100	OXTR FB -/- vs. OXTR +/- vs. WT	Resident Intruder	EN	EN *	EN
			17	0	OXTR FB -/- vs. OXTR +/- vs. WT	Resident Intruder	0.073	0.109	-0.412
Ragnauth et al.	2005	3	36	0					
			12	0	OXT -/- vs. WT	Feeding Challenge	3.410 *	-	-
			12	0	OXT -/- vs. WT	Resident Intruder	7.431 *	-	-
			12	0	OXT -/- vs. WT	Infanticide	EP *	-	-
Sala et al.	2011	1	20	100	OXTR -/- vs. OXTR +/+	Neutral Arena	0.868 *	-	-
Sala et al.	2013	1	29	100	OXTR -/- vs. OXTR -/+ vs. OXTR +/+	Neutral Arena	1.486 *	-	-
Takayanagi et al.	2005	3	53	100					
			18	100	OXTR -/- vs. OXTR +/+	Resident Intruder	1.199 *	-1.423 *	1.052 *
			20	100	OXT -/- vs. OXT +/+	Resident Intruder	-0.534	0.314	-0.425
			15	100	OXT -/- vs. OXT +/+	Resident Intruder	1.201 *	-1.097 *	1.613 *
Winslow et al.	2000	2	43	100					
			27	100	OXT -/- vs. WT	IIA	0.806 *	-	-
			16	100	OXT -/- vs. WT	Resident Intruder	2.130 *	-	-

Note. OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene, +/+ = no genetic knockout, +/- = heterozygous genetic knockout, -/- = homozygous genetic knockout, WT = wild type, FRSE = Free roam social exploration, IIA = Isolation induced aggression, EN = Extreme negative score without standard deviation, EP = Extreme positive score without standard deviation, Effect sizes reflect WT vs. KO contrasts,

* = Statistically significant results.

Table 3. Subgroup Analyses of Endogenous Oxytocin Effects on Attack Frequency

Subgroups	Sample		Meta Analysis					
	k	n	Hedges' g	SE	Z	p	95% CI LL	95% CI UL
Genetic Manipulation								
OXT	7	157	0.195	0.407	0.477	0.633	-0.605	0.994
OXTR	7	171	0.849	0.192	4.429	<0.001	0.473	1.225
OXTR FB	4	77	-0.296	0.341	-0.867	0.386	-0.963	0.372
Paradigm								
Resident Intruder	13	280	0.460	0.256	1.796	0.073	-0.042	0.963
Neutral-Arena	3	79	0.627	0.537	1.168	0.243	-0.425	1.679
Other	2	46	-0.129	0.931	-0.139	0.890	-1.954	1.695
Parental Mutation								
Heterozygous	12	267	0.294	0.276	1.066	0.286	-0.247	0.835
Homozygous	1	15	1.201	0.529	2.271	0.023	0.164	2.238
Mixed	4	103	0.455	0.555	0.819	0.413	-0.634	1.544
Unspecified	1	20	0.868	0.448	1.938	0.053	-0.010	1.746
Intruder Strain								
Different	16	358	0.468	0.214	2.181	0.029	0.047	0.888
Same	1	28	1.234	0.515	2.392	0.017	0.223	2.244
Unspecified	1	19	-1.080	0.474	-2.277	0.023	-2.010	-0.150
Sex								
Male	17	388	0.443	0.231	1.917	0.055	-0.010	0.895
Female	1	17	0.073	0.517	0.141	0.888	-0.941	1.088

Note. k = number of independent samplings, n = collective sample size, SE = standard error, LL = lower limit, UL = upper limit, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Table 4. Subgroup Analyses of Endogenous Oxytocin Effects on Attack Latency

Subgroups	Sample		Meta Analysis					
	k	n	Hedges' g	SE	Z	p	95% CI LL	95% CI UL
Genetic Manipulation								
OXT	5	114	0.082	0.331	0.248	0.804	-0.567	0.731
OXTR	2	38	-1.516	0.352	-4.307	<0.001	-2.206	-0.826
OXTR FB	3	55	0.065	0.337	0.194	0.846	-0.595	0.726
Paradigm								
Resident Intruder	8	158	-0.484	0.313	-1.543	0.123	-1.098	0.131
Neutral-Arena	1	30	-0.111	0.439	-0.252	0.801	-0.971	0.750
Other	1	19	1.088	0.475	2.292	0.022	0.158	2.019
Parental Mutation								
Heterozygous	7	132	-0.239	0.427	-0.560	0.576	-1.076	0.598
Homozygous	1	15	-1.097	0.522	-2.101	0.036	-2.121	-0.074
Mixed	2	60	0.010	0.311	0.031	0.975	-0.599	0.618
Strain								
Different	9	188	-0.431	0.273	-1.582	0.114	-0.966	0.103
Unspecified	1	19	1.088	0.475	2.292	0.022	0.158	2.019
Sex								
Male	9	190	-0.315	0.328	-0.960	0.337	-0.958	0.328
Female	1	17	0.109	0.518	0.211	0.833	-0.906	1.124

Note. k = number of independent samplings, n = collective sample size, SE = standard error, LL = lower limit, UL = upper limit, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Table 5. Subgroup Analyses of Endogenous Oxytocin Effects on Attack Duration

Subgroups	Sample		Meta Analysis					
	k	n	Hedges' g	SE	Z	p	95% CI LL	95% CI UL
Genetic Manipulation								
OXT	5	114	-0.219	0.419	-0.522	0.602	-1.042	0.604
OXTR	2	38	1.082	0.332	3.260	0.001	0.432	1.733
OXTR FB	4	77	-0.474	0.341	-1.389	0.165	-1.144	0.195
Paradigm								
Resident Intruder	9	180	0.228	0.359	0.636	0.525	-0.475	0.931
Neutral-Arena	1	30	-0.608	0.448	-1.352	0.176	-1.487	0.272
Other	1	19	-0.802	0.461	-1.740	0.082	-1.705	0.101
Parental Mutation								
Heterozygous	8	154	0.001	0.347	0.003	0.998	-0.679	0.681
Homozygous	1	15	1.613	0.560	2.878	0.004	0.515	2.711
Mixed	2	60	-0.646	0.318	-2.029	0.042	-1.270	-0.022
Strain								
Different	10	210	0.120	0.326	0.367	0.714	-0.520	0.759
Unspecified	1	19	-0.802	0.461	-1.740	0.082	-1.705	0.101
Sex								
Male	10	212	0.068	0.339	0.201	0.841	-0.597	0.733
Female	1	17	-0.412	0.523	-0.788	0.430	-1.437	0.613

Note. k = number of independent samplings, n = collective sample size, SE = standard error, LL = lower limit, UL = upper limit, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Table 6. Distribution of Significant Results

Genetic Mutation	Total Experiments	Significant Increase	Significant Decrease	Null Results
OXT	7 (10)	3 (6)	3 (3)	1 (1)
OXTR	7	5	0	2
OXTR FB	4	0	2	2

Note. Studies with at least one significant outcome were classified as significant results; OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene, numbers in parentheses include results of removed publication.

Figure 1. PRISMA Flowchart of Study Selection Process

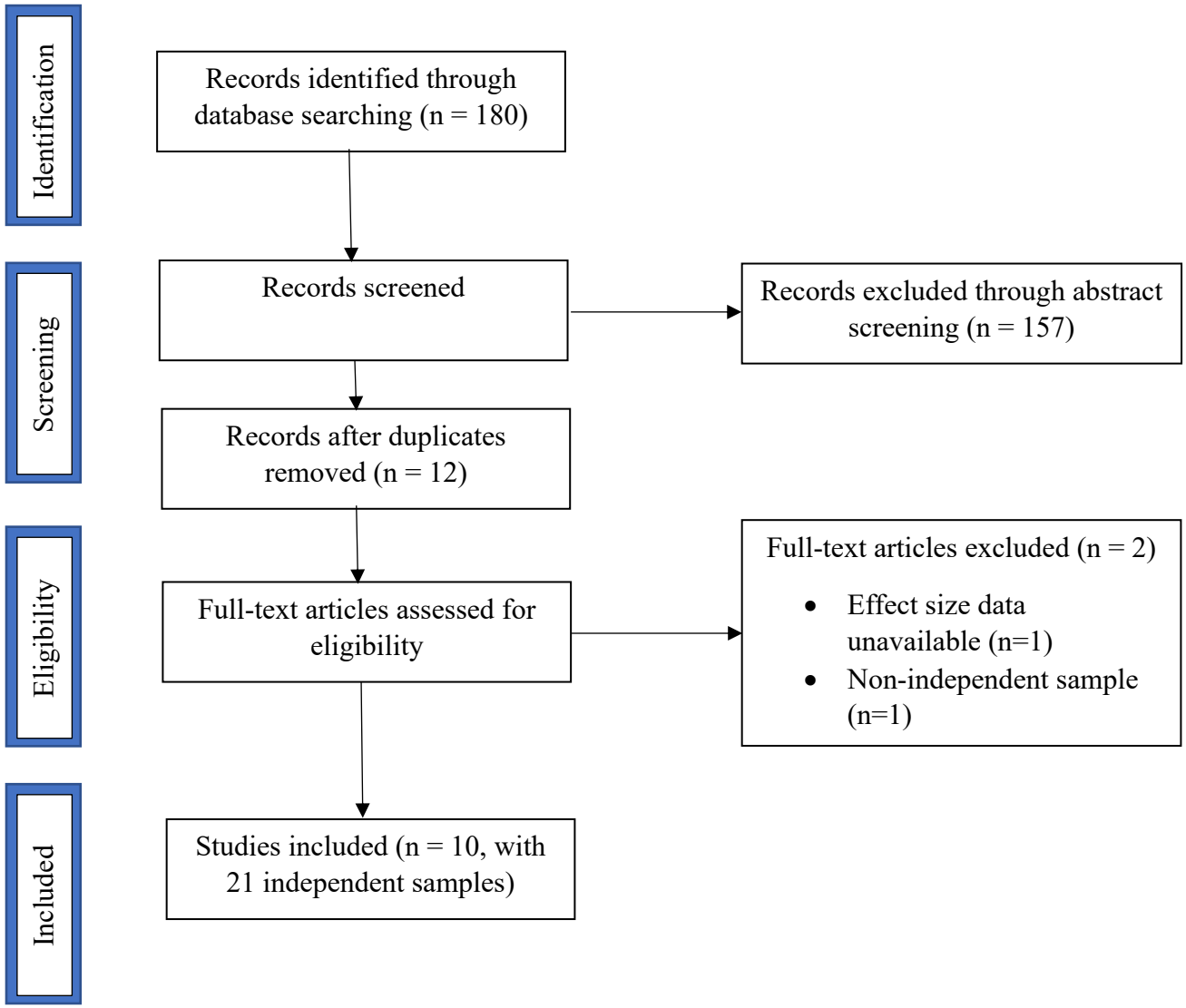


Figure 2. Funnel Plot of Attack Frequency

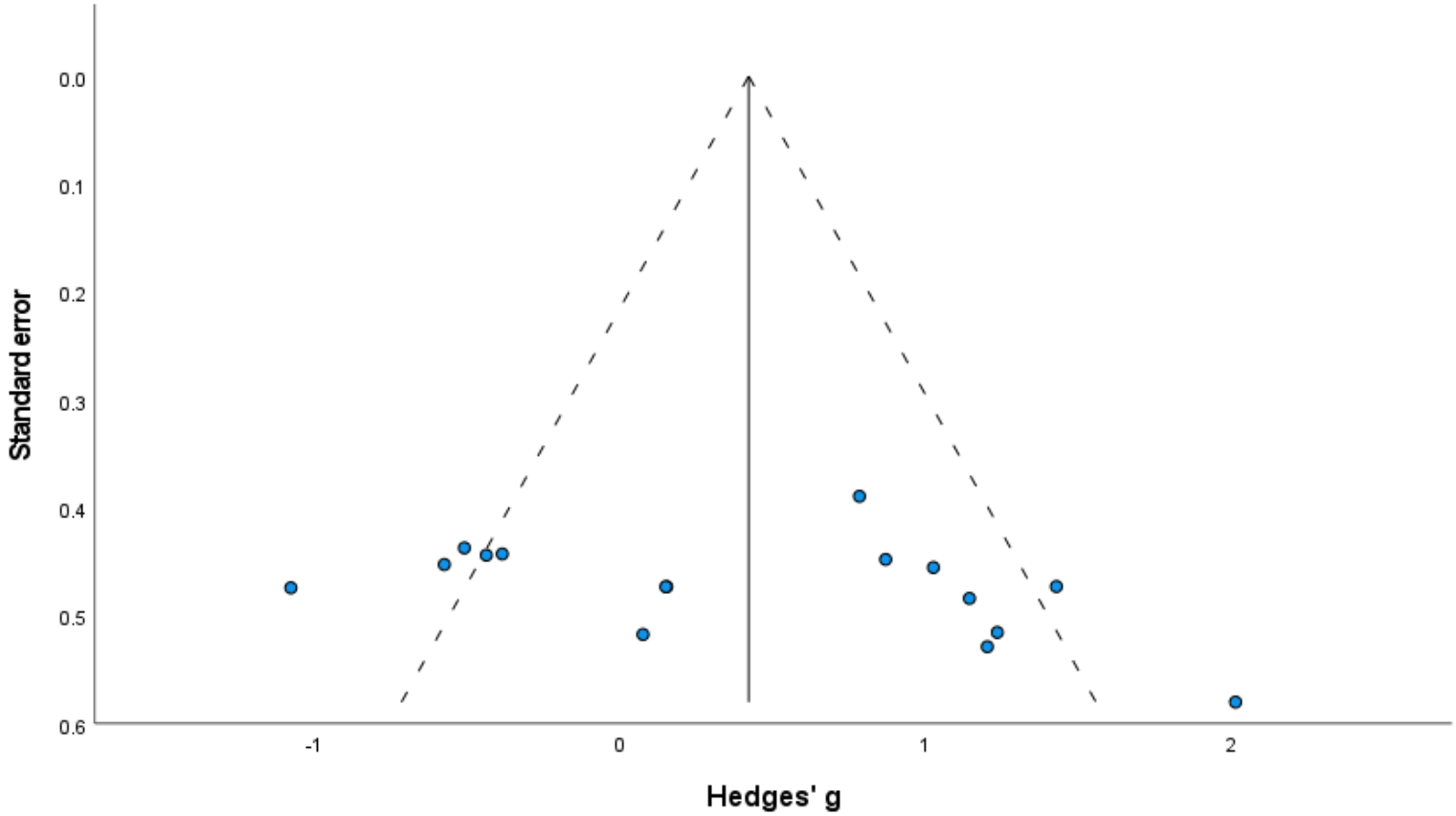


Figure 3. Funnel Plot of Attack Latency

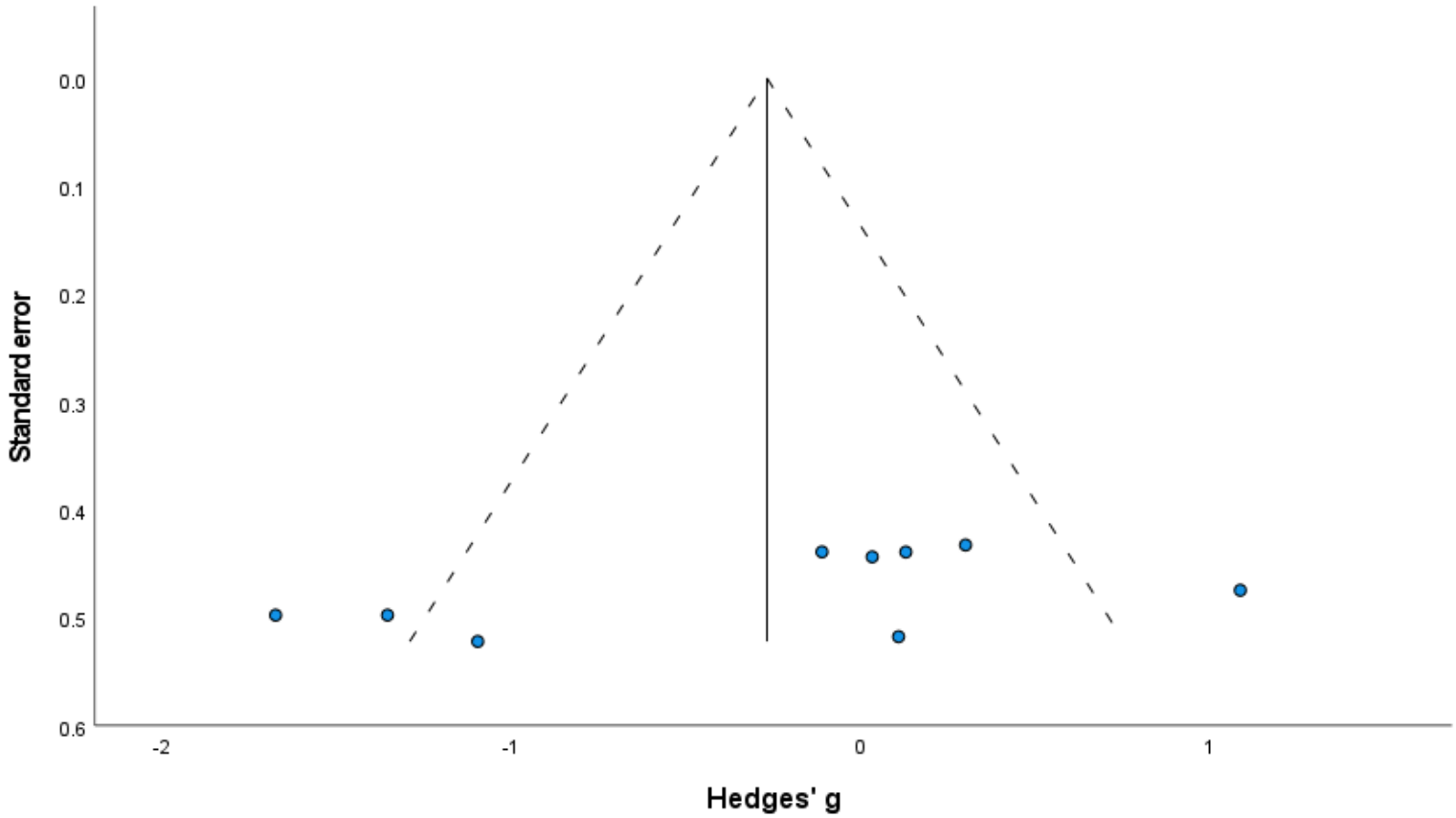


Figure 4. Funnel Plot of Attack Duration

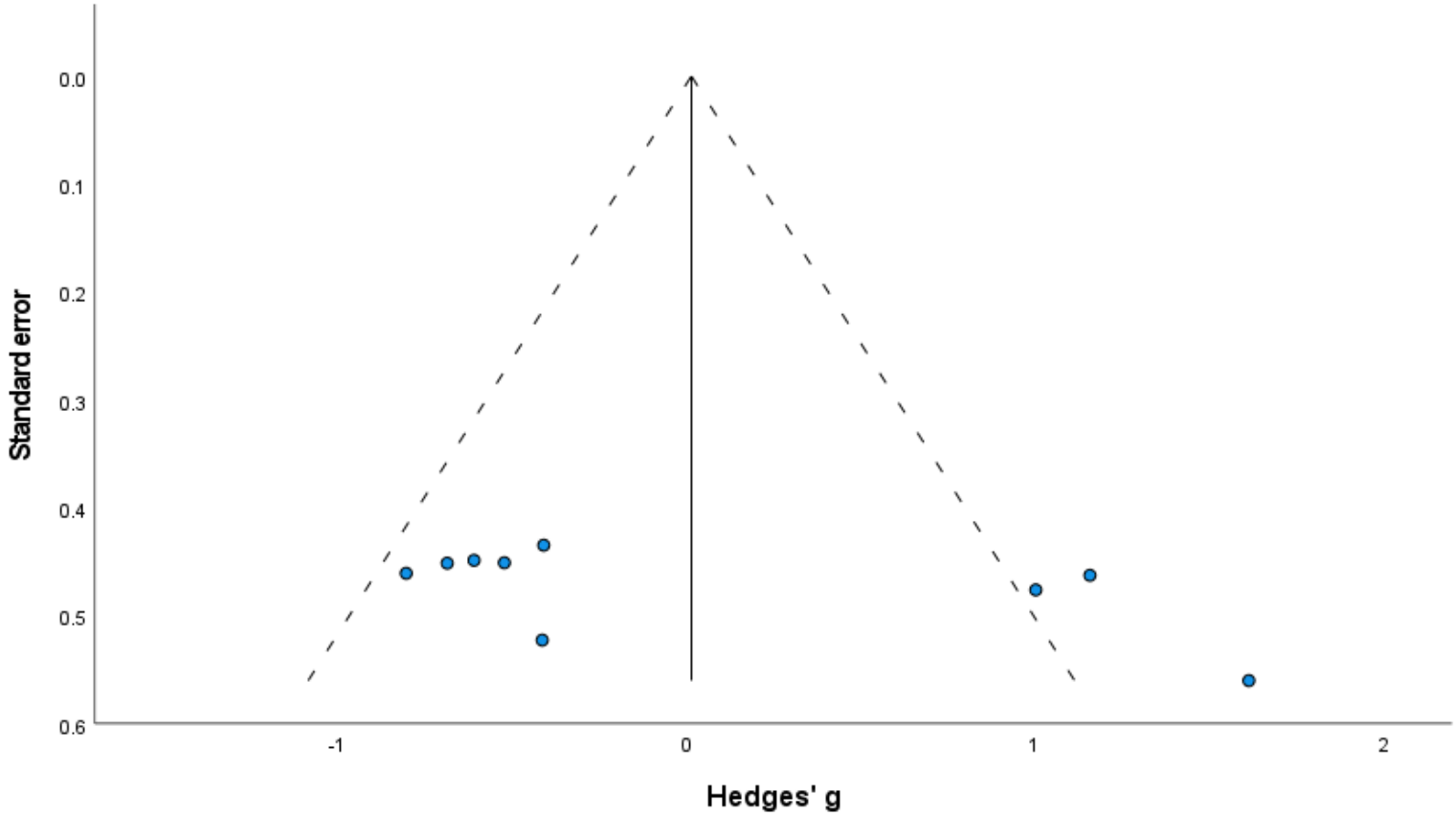
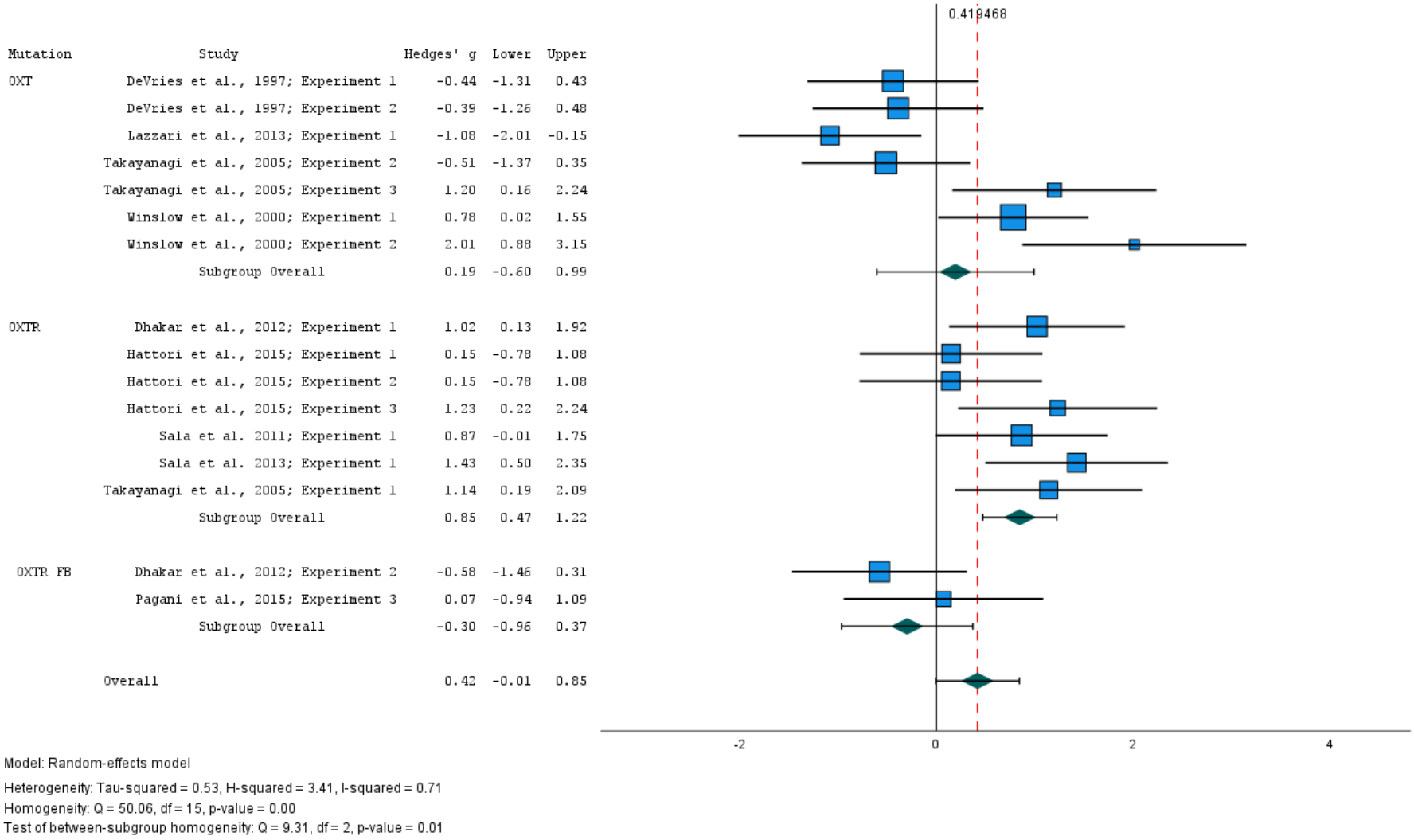
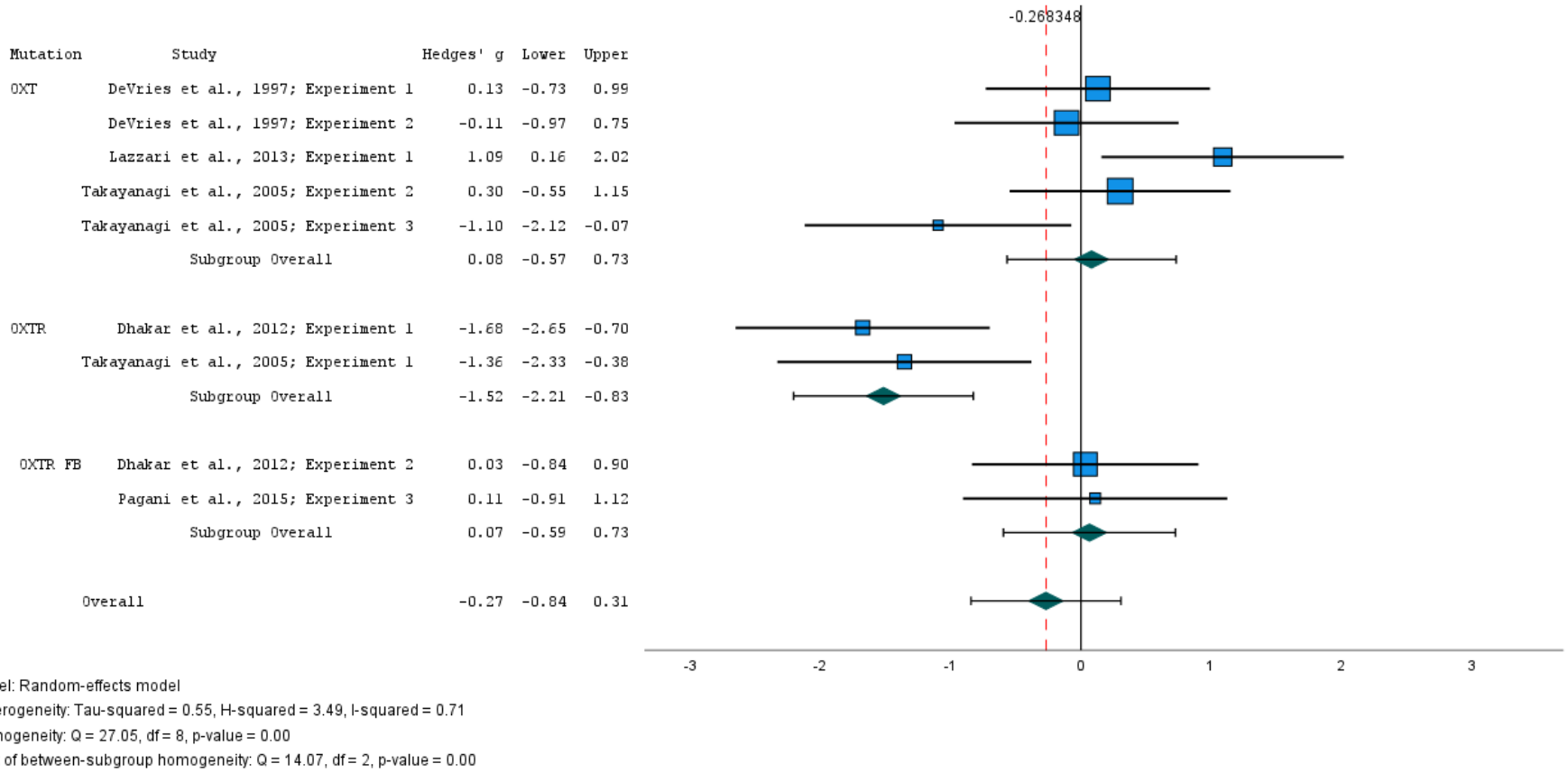


Figure 5. Forest Plot of Attack Frequency Separated by Genetic Manipulation



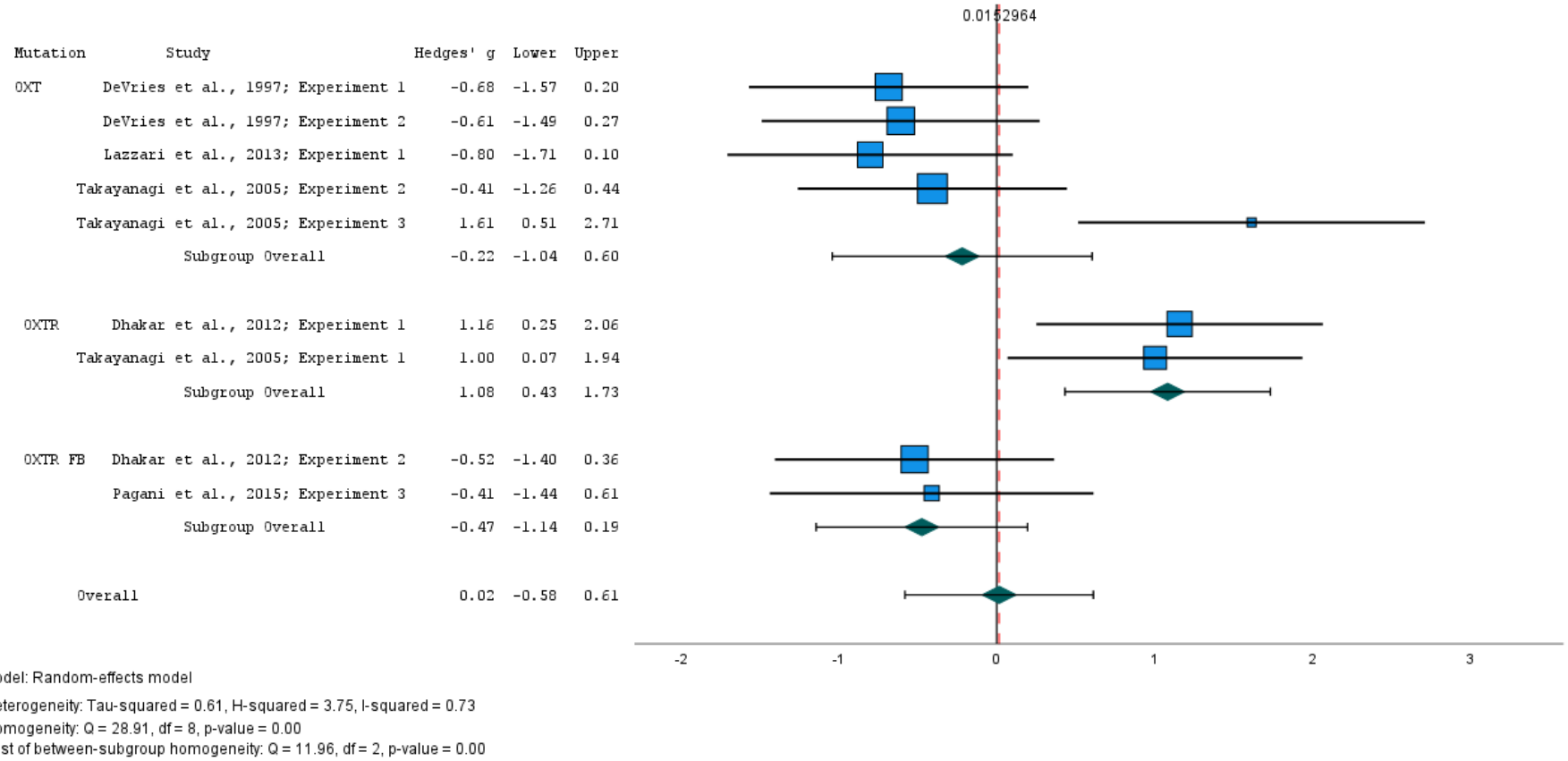
Note. Effect sizes of attack frequency contrasting oxytocin knockout mice to wild type mice, positive values indicate a greater number of aggressive behaviours, error bars represent 95% confidence intervals, diamond and dotted line represent overall effect size across studies, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Figure 6. Forest Plot of Attack Latency Separated by Genetic Manipulation



Note. Effect sizes of attack latency contrasting oxytocin knockout mice to wild type mice, positive values indicate a longer delay before the onset of aggressive behaviours, error bars represent 95% confidence intervals, diamond represent an dotted line overall effect size across studies, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Figure 7. Forest Plot of Attack Duration Separated by Genetic Manipulation



Note. Effect sizes of attack duration contrasting oxytocin knockout mice to wild type mice, positive values indicate a longer duration of aggressive behaviours, error bars represent 95% confidence intervals, diamond and dotted line represent overall effect size across studies, OXT = oxytocin-neurophysin gene, OXTR = oxytocin receptor gene, OXTR FB = conditional oxytocin receptor forebrain gene.

Transition Paragraph

Our review of the animal literature has shown a clear association between endogenous OT and aggressive behaviours in male mice. We found that this association was heavily influenced by developmental factors, wherein a prenatal lack of OT exposure produces large increases in aggression whereas a postnatal lack of OT exposure produces moderate, statistically non-significant decreases in aggression. Additionally, and in keeping with the broader OT literature, we found that these effects were further moderated by contextual and individual factors. Specifically, we found that intrastrain aggression was especially amplified following a disruption to the OT system, which suggests reduced in-group favoritism when endogenous OT production or binding is eliminated. Interestingly, this finding is consistent with more recent human OT research that has found that OT is central to in-group biases (e.g.: De Dreu et al., 2012). Our results also indicated that behavioural paradigms that best recreate a naturalistic competitive challenge (i.e., food scarcity and territorial intrusions) also elicit the greatest aggressive responses in OT deficient mice. In sum, we have found compelling evidence linking endogenous OT to adulthood aggression, at least in male mice, and have identified key variables that modulate this relation.

An important next step in this line of research would be to extend these findings to a human population. Clearly, the genetic manipulation of the OT system within humans is both impractical and unethical, but alternative approaches using exogenous OT administration may nevertheless fill this gap. In particular, approaches that stimulate the OT system, rather than impede endogenous functioning, would be better suited to human samples. Importantly, such methodologies would need to consider the greater degree of executive and rational control that underlies human, in contrast to non-human animal, behaviour. As such, one particularly viable approach would be to investigate the relation between OT and the cognitive biases that can contribute to externalizing behaviours. This avenue may prove especially fruitful given the already established relation

between exogenous OT and both self-perceptions (Cardoso et al., 2011; Colonnello & Heinrichs, 2014) and autobiographical memory (Cardoso et al., 2014, Wong et al., 2021). That is, existing research suggests that one way OT may be influencing human behaviour is by modifying aspects of the self-concept. To investigate this model in relation to aggression, we will examine the effects of OT administration on autobiographical memory recall, contrasting participants with high and low levels of self-reported aggressive behaviour. By examining the emotional valence of recalled events, we could in turn examine the relation between potential biases in autobiographical recall and self-reported externalizing behaviours. The administration of exogenous OT would further allow us to explore the impact of OT availability on such biases, and especially how they might differ across participants with different baseline profiles of externalizing behaviours. Lastly, such an approach would allow us to contrast the purely behavioural outcomes seen in animal models with the cognitive and self-referential outcomes that are particularly meaningfully to humans.

Chapter 3: Examining Interactions between Self-Reported Aggression and Intranasal Oxytocin: A Study of Autobiographical Memory

Abstract

Autobiographical memories (AMs) are believed to play a critical role in the preservation of a stable self-concept. Consequently, biases in AM retrieval can influence self-perceptions and are a central cognitive bias in the maintenance of affective disorders. Although similar biases are also observed in individuals with externalizing problems, research investigating the AM retrieval biases of aggressive individuals is limited. Using a validated cued-AM-retrieval task, we examined AM production across individuals with different degrees of self-reported aggression. Additionally, given that the nonapeptide oxytocin (OT) is known to alter self-perceptions, AM retrieval, and social behaviour, we investigated the effects of intranasal OT administration on patterns of AM retrieval across two different social contexts. We found that aggressive participants struggled to recall specific autobiographical events in response to positive cue words, which may reflect a bias towards the retrieval of negative memories of past events. Following OT administration, the retrieval of specific AMs in response to positive cue words was selectively improved in high-aggression participants, exclusively within a social experimental context. We also found that OT administration resulted in high-aggression participants rating the emotional valence of their recalled AMs less negatively in a social context, but less positively in a non-social context. Taken together, these findings replicate some of the AM retrieval biases previously reported in populations at risk for externalizing behaviours and provide further support to the emerging body of evidence that OT can alter patterns of AM retrieval. Additionally, our findings indicate important contextual and individual variability in OT's effects, in keeping with the broader OT literature. Namely, that OT selectively modifies AM retrieval in individuals prone to negative AM biases, uniquely within a social environment.

Introduction

Autobiographical memories (AMs) are recollections of past lived events and the crux of episodic memory; this memory system, distinct from other forms of memory, allows us to revisit and re-experience specific episodes from our past (Tulving, 2002). However, some researchers suggest that these memories are much more than discrete recollections of past experiences. AMs are fundamental to effective problem solving, organized and goal-directed behaviours, maintaining and evaluating interpersonal relationships, and, perhaps most importantly, to maintaining a persistent and coherent self-identity (Bluck, 2003; Bluck & Habermas, 2001; Conway, 2005; Conway et al., 2004; Pollock & Williams, 2001). That is, how we remember our pasts has a remarkable influence on how we understand and navigate our present. Given that AM is such a central component in the maintenance and modification of self-related schemas, it is then unsurprising that AM dysfunctions are characteristic of certain forms of psychopathology. In particular, overgeneral AM – the tendency to recall extended or generalized categories of events (e.g.: I get sad when it rains) rather than specific recollections of distinct autobiographical episodes (e.g.: It rained last Tuesday)– has been shown to be a central feature of several psychiatric disorders.

Overgeneral AM was first identified in suicide attempters (Williams & Broadbent, 1986). Since then, this pattern of AM recall has become a defining cognitive feature of major depressive disorder (Brittlebank, et al., 1993; Williams & Scott, 1988; Williams et al., 2007) and PTSD (Schönfeld & Ehlers, 2006; Schönfeld et al., 2007). Overgeneral AM has also been observed in samples with subclinical levels of dysphoria (Matsumoto et al., 2020; Romero et al., 2014) and complicated grief (Boelen et al., 2010; Maccallum & Bryant, 2011). Given these findings, overgeneral AM may represent a risk factor for affective disorders (Brittlebank et al., 1993; Rawal

& Rice, 2012). In fact, overgeneral AM is believed to precede affective symptoms (Gibbs & Rude, 2004; Rawal & Rice, 2012) and has been shown to be predictive of a worse prognosis and more severe symptomatology in persons with major depressive disorder (Gibbs & Rude, 2004; Hermans et al., 2008; Raes et al., 2006). Importantly, previous works have also found that overgeneral recall persists even when depressive episodes remit (Brittlebank et al., 1993; Peeters et al., 2002) and that AM deficits exist even in the absence of more generalized semantic memory deficits (Soderlund et al., 2014). In short, overgeneral AM recall is not simply a symptom of depressive pathology, but rather is a facet of cognition that predisposes individuals to multiple types of psychiatric disorders. While this association between overgeneral AM and affective disorders is well documented, the mechanisms underlying this relation are still not fully understood.

One viable hypothesis is that overgeneral AM recall is a reflection of the depressogenic cognitive biases that are characteristic of affective disorders. Existing literature has shown that individuals at-risk for subsequent depression or those experiencing current depressive episodes display a wide array of attentional and interpretational biases that maintain their negative beliefs about themselves, those around them, and the world at large. In brief, such individuals reliably demonstrate biases in attention, working memory, long-term memory, and subjective interpretations that all individually and interactively contribute to symptom severity (see Everaert & Koster, 2020 and Everaert et al., 2020 for reviews). For instance, they display a hypervigilance for negative information from which they have difficulty disengaging, a negative bias in the interpretation of ambiguous information, a tendency to ruminate on negative information, and negative expectations about their own practical and interpersonal efficacy (Duque & Vazquez, 2015; Ellenbogen & Schwartzman, 2009; Lavender & Watkins, 2004; Strunk et al., 2006; Rude et al., 2002). These biases, in turn, facilitate the maintenance of negative beliefs and schemas by

directing focus towards confirmatory evidence and away from contradictory evidence. In the same way, overgeneral recall for past events may interfere with the retrieval of counterevidence for these negative cognitions, thereby reinforcing the maladaptive beliefs at the heart of affective disorders. This hypothesis is formalized within the CaR-FA-X model of memory retrieval, which stipulates that overgeneral AM recall may be an emergent facet of these depressogenic biases (see Williams, 2006 or Sumner, 2012 for reviews). To summarize, this model suggests that three processes contribute to reduced AM specificity, both alone and in interaction: capture and rumination (CaR), functional avoidance (FA), and impaired executive control (X). That is, perseverative thinking, maladaptive emotion regulation strategies, as well as reduced efficiency of and control over executive processes can each individually result in episodic memory searches that are prematurely truncated at a more general level; when all three of these processes co-occur, a pattern common in affective disorders, the retrieval of specific AM events becomes impaired. In turn, overgeneral AM recall may reinforce depressogenic biases by facilitating the perspective that negative events are generalized and pervasive.

For this reason, overgeneral AM recall might be a viable target for intervention. A growing body of evidence suggests that patterns of overgeneral recall can be mitigated following treatment, particularly cognitive behavioural therapy. Previous findings include the reduction of overgeneral recall following treatment in those suffering from major depressive disorder (McBride et al., 2007; Williams et al., 2000), PTSD (Sutherland & Bryant, 2007), and complicated grief (Maccallum & Bryant, 2011). Moreover, reduced overgeneral recall was strongly associated with degree of symptom reduction, suggesting that overgeneral memory is both modifiable and directly related to psychiatric improvements. Importantly, there is also growing evidence that overgeneral AM recall itself can be directly targeted by cognitive interventions. Specialized training to improve AM

retrieval (Moradi et al., 2014; Raes et al., 2009) as well as cognitive techniques to reduce rumination (Raes et al., 2008; Watkins et al., 2000) have been shown to reduce overgeneral AM recall in both clinical and non-clinical samples. The finding that overgeneral AM can be directly targeted by therapeutic interventions is of interest, as it suggests a novel approach to symptom reduction. Given that overgeneral AM recall is a transdiagnostic phenomenon, a comprehensive understanding of this maladaptive cognitive process is likely to be relevant to different forms of psychopathology.

In particular, there are numerous parallels between the cognitive biases seen in affective disorders and those found in individuals with heightened levels of aggression or hostility (see Owen, 2011 for a review). For example, high trait anger and hostility participants show a greater predisposition towards rumination than their low-anger peers (Martin & Dahlen, 2005; Wang et al., 2018; Wilkowski & Robinson, 2010), although the valence of their ruminative processes tends to be more focused on anger and frustration rather than sadness and disappointment. Nonetheless, both those with affective disorders and high aggression display difficulties disengaging from unpleasant thoughts. Individuals high in aggression also demonstrate attentional biases towards anger-related and potentially threatening stimuli (Parrott et al., 2005; Smith & Waterman, 2003; Van Honk et al., 2001). They also exhibit a tendency to interpret ambiguous stimuli as threatening or dangerous and to appraise ambiguous situations as indicative of antagonism (Hazebroek et al., 2001; Maoz et al., 2016; Wilkowski & Robinson, 2010). In turn, these biases are predictive of heightened verbal and physical aggression (Anestis et al., 2009; Denson et al., 2011; Maxwell, 2004). Additionally, participants high in trait anger and hostility are more likely to engage in avoidance-based coping strategies than low-hostility controls (McCormick & Smith, 1995;

Vandervoot, 2006). Given the nature of these parallel biases, one might predict similar AM deficits between those with affective disorders and high trait anger.

Unfortunately, published research on this topic is limited. For instance, individuals high in trait anger are more likely to recall memories with anger-related content (Hung & Bryant, 2016) and to rate their own autobiographical recollections as less pleasant than low-anger controls (Wenzel & Jordan, 2005). To our knowledge, no research to date has specifically investigated overgeneral recall in participants with high aggression or hostility, but some research using criminal offenders is available. Offenders generate fewer specific positive AMs and a greater number of overgeneral negative AMs compared to non-incarcerated controls (Neves & Pinho, 2015; Neves & Pinho, 2018). Moreover, they also generated negative recollections more quickly and described them as having a greater emotional intensity and as being more significant to their life history than controls. In sum, although research on the AM patterns of violent and aggressive individuals is limited, findings to date suggest that similar AM processes occur in persons having internalizing and externalizing problems.

A recent avenue of research in our understanding of AM retrieval is the nonapeptide oxytocin (OT). Although best known for its critical role in pair bonding and maternal behaviours in animals (e.g.: Amico et al., 2004; Insel & Hulihan, 1995), intranasal OT administration has also been found to elicit a wide range of changes on human social cognition (see Bakermans-Kranenburg & van IJzendoorn, 2013 or Van IJzendoorn & Bakermans-Kranenburg, 2012 for reviews). Importantly, these changes have been found to be highly context-dependant, with OT administration producing opposite effects under different social environments. For instance, exogenous OT can both increase and decrease trust, depending on the nature of the social interaction and expectations about the interaction partner (see Nave et al., 2015 for a review); this

suggests that OT can both enhance and diminish cooperation according to social and environmental cues. In sum, OT has been associated notable but variable changes to social cognition, which may also extend to AM.

While research investigating the relation between OT and AM is sparse, studies have found that intranasal OT administration can alter self-related schemas. Specifically, OT administration, compared to placebo, increased positive self-perceptions, particularly for aspect of the self that are related to kindness and social affiliation (Cardoso et al., 2011; Colonnello & Heinrichs, 2014). In keeping with the association between self-related schemas and autobiographical recall, OT has also been shown to alter patterns of AM retrieval. To illustrate, a single dose of intranasal OT reduced overgeneral AM recall in healthy participants (Cardoso et al., 2014); this same project also found that participants rated their social AMs more positively following intranasal OT than those retrieved under placebo. Additionally, OT administration has also been found to reduce pre-existing attentional biases in participants suffering from depression (Ellenbogen, 2011), social anxiety (Clark-Elford et al., 2014), eating disorders (Kim et al., 2018; Kim et al., 2014), and borderline personality disorder (Bertsch et al., 2013), often resulting in attentional profiles more similar to those of healthy controls. However, as with many findings within the OT literature, the effects of OT administration may be heavily moderated by contextual and intra-individual factors (e.g.: Cardoso et al., 2016b; Wong et al., 2021; see Bartz et al., 2011 for a review). To illustrate, a recent study found that intranasal OT administration results in more vivid AM recollections, but only when completing an AM procedure while face-to-face with a research assistant (Wong et al., 2021); when completing a computerized version of the AM procedure void of social contact, no such effect was found. Rather, in the computerized non-social format, participants with elevated depressive symptoms recall AMs which they rated as more negative, an effect that was not

observed in low-depression participants or in the face-to-face social context. This suggests that, in the absence of a supportive social context, OT administration may worsen, rather than alleviate, existing biases.

Given the above-mentioned pattern of results, the aims of this project are three-fold. First, we aim to investigate, for the first time, the relationship between self-reported aggression and overgeneral AM recall in a non-incarcerated community sample. We anticipate replicating previous findings produced in criminal samples, in which overgeneral AM recall is elevated for positive cue words. Second, we aim to contrast self-ratings of emotional valence for AM content between high- and low-aggression participants. We anticipate replicating the finding that high trait-anger participants rate their autobiographical recollections more negatively than lower-anger controls using, for the first time, measures of behavioural aggression rather than emotional anger. Lastly, we aim to investigate, for the first time, the effects of intranasal OT administration on patterns of AM recall, contrasting high- and low-aggression participants in both a social and non-social context. We predict that OT administration will reduce overgeneral recall for high-aggression participants in the social condition; in contrast, we predict that overgeneral recall will be amplified in the non-social condition. Overall, we hope to extend the current understanding of AM retrieval in aggressive individuals, which could serve as a foundation for future research and intervention.

To accomplish these goals, we conducted a secondary analysis of data collected and published by Wong and colleagues (2021), which investigated the self-reported vividness and emotional valence of AMs in relation to depressive symptomatology. Importantly, those variable were not included in any of our analyses and the data reported in the present manuscript are novel, focusing solely on aggression and AM, and thus have not been published previously.

Method

Participants

Sixty-three participants (32 female) between the ages of 18 and 35 ($M = 24.60$, $SD = 4.22$) were recruited through online advertisements (e.g., Craigslist). Exclusion criteria included current use of tobacco or prescription drugs, current or past use of illicit drugs (excluding cannabis, which required one-year of abstinence), severe medical conditions, history of receiving psychiatric or psychological services, and suspected pregnancy in women. Only participants who were fluent in English were included in the study. Of the 25 females not taking the oral contraceptive pill, six were in the follicular menstrual phase and 19 were in the luteal phase across all test sessions. See Table 1 for a summary of participant demographic data.

Materials and Measures

Oxytocin Nasal Spray

All doses of OT (Syntocinon, *Novartis*, Basel, Switzerland) and placebo (saline) were self-administered using a nasal-spray bottle (0.10 cc/spray). Both the participants and the experimenter were blind to the contents of the nasal spray. Oxytocin was contained in 5 mL of solution comprised of purified water and other inactive substances. The placebo used in this study was identical to the solution listed above without the chemically active ingredient (OT).

Achenbach System of Empirically Based Assessment – Adult Self-Report

The Adult Self-Report (ASR) is part of the Achenbach System of Empirically Based Assessment tools (Achenbach and Rescorla 2003). It is a self-report measure which examines adaptive functioning, behavioural problems, and symptoms of psychopathology. In it, participants rate the accuracy of statements regarding their thoughts, feelings, and behaviours over the previous six months using a three-point response scale (from *0 = not true* to *2 = very true or often true*). It

consists of 120 items (e.g.: "*I damage or destroy things*" and "*I threaten to hurt people*") and responses are used to compute eight syndrome scales; each item has a unique loading onto these scales based on prior factor analyses. For the present project, only the *Aggressive Behaviour* syndrome scale was used, which is a measure of the self-reported frequency of aggressive behaviours (e.g.: "*I physically attack people*"). Internal consistency within our sample was 0.94.

Autobiographical Memory Test

The Autobiographical Memory Test (AMT) is a test of self-generated episodic memory recall (Williams & Broadbent, 1986). It is traditionally administered in a face-to-face format; the experimenter provides a verbally presented cue word to which the participant is tasked with providing a specific autobiographical memory. Cue words are valenced as either positive, negative, or neutral (e.g.: *happy, lonely, chair*). Participants are informed that a specific memory is one that refers to a discrete event contained within a single 24-hour interval; any recollections that do not meet these criteria are rated as overgneral. The experimenter maintains a neutral demeanor throughout the task.

In this study, we used a modified version of the AMT which manipulated social context (Cardoso et al., 2016b). Specifically, cue words were either presented verbally by a same-sexed experimenter in-person (social condition) or presented visually on a computer to participants who were alone in a room that was being monitored remotely (non-social condition). Participants recalled memories in response to 30 unique cue words in each condition that alternated between positive, negative, and neutral valence. As such, 120 cue words were randomised into four word-lists that were counterbalanced across both social conditions and across two test sessions (OT, placebo). AMT sessions were recorded and recollections were subsequently coded as either specific or overgeneral by two independent raters; disagreements between raters were discussed

until consensus was reached. Additionally, participants were asked to rate the positive and negative valence of each of their recollections using a 6-point Likert scale (from *1 = not at all* and *7 = extremely*). Participants were also asked to rate the frequency with which these recollections were contemplated as well as the vividness of each recollection using a 100-point visual analogue scale, which are not reported here. See Table 2 for a summary of the AMT data.

Procedure

Eligible participants were scheduled for two laboratory visits one week apart, with the time of day consistent across test sessions. Females were scheduled for both sessions on days that they were taking the active oral contraceptive pill to control for variations in oestrous hormones. Females not taking the oral contraceptive pill were scheduled for both testing sessions within 0-11 or 17-25 days of the first day of menstruation. Accurate scheduling within either phase was achieved by having females contact the laboratory on the first day of their menstruation.

Prior to their first test session, participants completed a questionnaire battery. This battery included the ASR, as well as additional measures that were part of a larger data collection (Cardoso et al., 2016b; Wong et al., 2021). Upon arrival, participants self-administered 24 IU of intranasal OT or placebo, with the order of administration counter-balanced across participants. Drug administration was conducted in accordance with published guidelines on intranasal oxytocin administration (Guastella et al., 2013). This was followed by a 30-minute rest period, during which participants were left on their own in a quiet room. They were provided with neutral magazines and allowed to use their cellular phones during this time but were specifically asked to refrain from any social media use. Participants then completed a 60-minute eye-tracking experiment, which is not reported here. The eye tracking experiment included an anti-saccade task, which assessed participants' ability to shift away from an emotional or neutral facial expression, as well as tasks

assessing attention to facial features (eyes, mouth) of a single face presentation, and a free-viewing task with a quadrant of multiple faces expressing different emotions (see Boyle et al., 2022 for a more detailed summary). Lastly, participants completed the social and non-social AMT as described above. The order of test conditions was counter-balanced across participants. At the end of the first session, participants were scheduled for the second test session, which was identical to the first except for the drug condition. At the end of the second test session, participants were debriefed and remunerated $70 CAD. This project was approved by the Human Research Ethics Committee at Concordia University (Montreal, Canada). Informed written consent was obtained for all participants.

Statistical Analyses

Main effects of aggression on autobiographical memory recall were investigated using a series of simple linear regressions that used only placebo condition scores. Moderation of OT effects by aggression were investigated using the MEMORE macro for SPSS (Montoya, 2018). This specialized script automatically computes and contrasts difference scores across different levels of the moderating variable. This macro follows the best recommended guidelines for within-subject moderation (Montoya & Hayes, 2017). Continuous moderators were centered; this is the recommended approach for estimating moderation in within-subject designs (Judd, Kenny, & McClelland, 2001). All analyses were run using SPSS version 22 (IBM Software, Armonk, NY).

Results

Data Integrity

A total of one outlier (approximately 1.5% of all data) was observed within the independent variable included in these analyses; this scores was retained, as the primary goal of this study was to investigate the effects of elevated aggression scores. Scores for eleven dependent variable

outliers (approximately 0.5% of all data) were reduced to three standard deviations above the mean. Skewness and kurtosis were verified for all variables and were found to be within the acceptable ranges (i.e., absolute values of less than 3.0 and less than 10.0, respectively) as outlined by Kline (2009). Independence of residuals was investigated using the Durbin-Watson Test, which produced a test statistic of 1.91; this is in keeping with the acceptable range of 1.0 to 3.0, as outlined by Field (2009).

Main Effects of Aggression on Memory Specificity

The main effect of aggression on autobiographical recall was analyzed using a series of simple linear regressions examining placebo condition responses. For positive cue words, participants who scored higher on the ASR aggressive behaviour scale, $F_{(1,61)} = 8.506$, $p = .005$, adjusted $r^2 = .110$, recalled a greater number of overgeneral memories in the social condition than their lower aggression peers. These findings were specific to the social context and were not observed in the non-social condition, $F_{(1,61)} = 0.947$, $p = .334$, adjusted $r^2 = .001$.

For both neutral and negative cue words, no statistically significant associations between self-reported aggression and overgeneral memory were observed in either social condition. See Table 2 for a summary of the AMT data.

Main Effects of Aggression on Memory Valence

No statistically significant associations between self-reported aggression and participants' positive or negative valence ratings were observed in either social condition, for neither positive, neutral, nor negative cue words.

Moderation of OT Effects on Memory Specificity by Aggression

Moderation by aggression on the effects of OT administration was analyzed using a specialized script contrasting drug condition difference scores across levels of aggression

measures. For positive cue words, participants who scored higher on the ASR aggressive behaviour scale, $F_{(1,61)} = 5.822$, $p = .018$, $r^2 = .088$, produced fewer overgeneral memories in the social condition following OT administration, which was not observed in their lower aggression peers (Figure 1). These findings were specific to the social context and were not observed in the non-social condition, $F_{(1,61)} = 2.196$, $p = .143$, $r^2 = .035$.

For both neutral and negative cue words, no statistically significant moderation of overgeneral memory recall by self-reported aggression was observed in either social condition.

Moderation of OT Effects on Memory Valence by Aggression

For positive cue words, no statistically significant moderation of positive or negative valence ratings by self-reported aggression was observed in either social condition.

For neutral cue words, participants who scored higher on the ASR aggressive behaviour scale, $F_{(1,61)} = 4.456$, $p = .039$, $r^2 = .069$, rated their autobiographical memories less negatively in the social condition following OT administration, which was not observed in their lower aggression peers (Figure 2). These findings were specific to the social context and were not observed in the non-social condition, $F_{(1,61)} = 0.135$, $p = .714$, $r^2 = .002$. In contrast, statistically significant moderation was observed in the non-social condition for ratings of positive valence. Participants who scored higher on the ASR aggressive behaviour scale, $F_{(1,61)} = 5.415$, $p = .023$, $r^2 = .082$, rated their autobiographical memories less positively following OT administration, which was not observed in their lower aggression peers (Figure 3). These findings were specific to the non-social context and were not observed in the social condition, $F_{(1,61)} = 0.903$, $p = .345$, $r^2 = .014$.

Lastly, for negative cue words, no statistically significant moderation of positive or negative valence ratings by self-reported aggression was observed in either social condition. See Table 3 for a summary of moderation analyses.

Discussion

The purpose of this study was three-fold. We aimed to investigate the influence of elevated aggression on both the specificity and emotional valence of AM recollections in a non-clinical sample. We also aimed to investigate how intranasal OT administration might alter these recollections, while considering the differential effects of OT in social and non-social contexts. We predicted elevated overgeneral AM recall in response to positive cues for high-aggression participants, in keeping with previous findings obtained from criminal populations (Neves & Pinho, 2015; Neves & Pinho, 2018). We anticipated replicating the finding that high trait-anger participants rate their autobiographical recollections more negatively than their lower-anger peers using a measure of behavioural aggression rather than emotional anger (Wenzel & Jordan, 2005). Lastly, we predicted that intranasal OT administration would reduce discrepancies in memory specificity and valence ratings between high- and low-aggression participants in the social condition, but would instead amplify them in the non-social condition.

In keeping with our hypotheses, we successfully replicated the findings of elevated overgeneral recall in aggressive individuals. Specifically, we found that, under placebo, participants with higher levels of self-reported aggression produced a greater number of overgeneral recollections for positive cues in the social condition only. This finding is suggestive of an AM retrieval bias in high-aggression individuals, in which they have particular difficulty clearly recalling positive events from their past while showing no parallel issues recalling specific negative events. Given that AM retrieval biases are predictive of the severity and course of affective episodes in major depressive disorder (Gibbs & Rude, 2004; Hermans et al., 2008; McBride et al., 2007), it is plausible that the biases we observed here play a role in the maintenance of externalizing behaviours in hostile and aggressive individuals. That is, if one consistently

struggles to retrieve pleasant or otherwise emotionally positive recollections, they may begin to see themselves as prone to negative emotions and be more likely to behave in a congruent fashion.

One popular theory to explain overgeneral AM recall is the CaR-FA-X model, described previously. According to this model, overgeneral AM retrieval may represent an emergent facet of the cognitive biases that are characteristic of certain psychiatric conditions. Namely, this model stipulates that overgeneral recall reflects avoidance-based coping strategies, ruminative processes, and impaired executive functioning. That is, the CaR-FA-X model describes a reduced ability to voluntarily control top-down executive processes combined with a desire to avoid difficult or unpleasant recollections that may produce truncated searches resulting in overgeneral AM retrieval. There is theoretical support for this model – for example, overgeneral recall to negative cue words is heightened in individuals prone to avoidance coping, even in the absence of psychiatric diagnoses (Hauer et al., 2006; Hermans et al., 2005) – however, it is not congruent with our pattern of results. If one of the key functions of overgeneral AM recall is the avoidance of specific unwanted recollections, then one would expect overgeneral recall to be greatest following negative cues. In contrast, we observed heightened overgeneral recall for positive cues instead, in keeping with previous findings from incarcerated samples. Rather, this pattern of results is consistent with an alternative theoretical view of AM recall bias, the Self-Memory System (SMS) model. According to the SMS model, AMs that are congruent with current self-schemas and goals are more readily retrieved, as they help maintain one's sense of identity (Conway & Pleydell-Pearce, 2000); this retrieval bias then further solidifies that self-perception which promotes continued retrieval biases in the future. As such, if high-aggression individuals have a self-concept in which they see themselves as hostile and prone to negative emotions, then they would most easily retrieve negatively-cued recollections. In turn, positive events would be least congruent with

their self-schema and, as such, the most prone to overgeneral recall. That is, it may be difficult to retrieve a specific recollection for the word "happy" if one does not consider themselves to be a happy person. Thus, the SMS model may best account for overgeneral AM recall, at least in high-aggression individuals.

Of note, we anticipated that overgeneral recall following positive cue words would be greater for high-aggression participants in both social conditions, whereas our findings revealed elevated overgeneral recall in the social condition only. This selective difficulty retrieving specific positive autobiographical events within a social context may reflect the decreased social skills of high-aggression participants. Previous research has found that aggressive individuals demonstrate important deficits in their social competences and social problem solving (D'zurilla et al., 2003; Mayberry & Espelage, 2006). Completing a face-to-face task that requires candidness and the divulging of personal information may constitute a social challenge for high-aggression participants; this, in turn, could activate self-schemas related to social conflict and hostility further impeding the recollection of specific positive events. Likewise, the neutral demeanor of research assistant throughout the AMT procedure may have interacted with the interpretational biases seen in high-aggression individuals. That is, given that such individuals demonstrate a tendency to interpret ambiguous stimuli negatively (Maoz et al., 2016; Wilkowski & Robinson, 2010), it is plausible that the neutral and non-judgmental attitude of research assistants was perceived as indifference or even antagonism. Such biases could also have activated self-schemas related to social conflict. In keeping with the SMS model, this would subsequently facilitate the recall of self-schema-congruent AMs, which would be conflictual or otherwise negative recollections. Conversely, this effect could be diminished in the absence of a social challenge, explaining the lack of significant effects in the non-social condition.

Regarding self-ratings of emotional valence, our results did not support our hypothesis as we failed to replicate the previous finding of increased negative valence ratings in high trait-anger participants. This discrepancy between our findings and previously published results may reflect differences between samples. To date, research on the emotional valence or AM recollections in participants at risk of externalizing behaviours has been limited to two methodological approaches. The first involved participants scoring high on a measure of trait-anger (Wenzel & Jordan, 2005). Although evidence does suggest a strong association between emotional anger and behavioural aggression (e.g.: Hou et al., 2017, Kolla et al., 2016), more nuanced investigations have found this relation to be heavily moderated by additional variables. Impulsivity (Shorey et al., 2010; Wittmann et al., 2008), emotional dysregulation (Mancke et al., 2017), and attitudes towards others (Gaianu et al., 2020; Parrott & Zeichner, 2003) have all been found to interact with trait-anger in the prediction of aggressive behaviours. The second methodological approach to this research question has used incarcerated samples of criminal offenders. While criminality is a viable analogue for aggressive behaviour, it is a construct that also taps into to other form of externalizing pathology (e.g.: callousness, psychopathy). Moreover, these represent extreme forms of externalizing behaviour, which may relate to additional constructs, such as Machiavellianism or narcissism. Taken together, it is plausible that our specific community sample is representative of a unique set of factors that collectively failed to produce a significant discrepancy in valence ratings. For instance, it is possible that high-aggression participants in our sample were subject to maladaptive attitudes rather than emotional dysregulation, resulting in valence ratings that were more homogenous with their low-aggression peers. In the absence of a more comprehensive emotional and cognitive profile, it is impossible to disentangle the underlying factors that may have contributed to our lack of replication.

Importantly, the present study adds further evidence that OT's effects on social cognition are moderated by contextual factors (e.g.: Declerck et al., 2010) and inter-individual differences (e.g.: Bartz et al., 2019). We found that OT administration, relative to placebo, selectively reduced overgeneral AM recall following positive cues in the social condition among participants with high aggression. That is, the AM retrieval patterns of high-aggression individuals mirrored those of their low-aggression peers following OT administration. In addition, we found robust contextual effects for valence ratings that were in keeping with our hypotheses. Namely, during the social administration of the AMT, high-aggression participants rated the valence of their recalled AMs less negatively under OT, compared to placebo. Conversely, in the computerized (non-social) administration of the task, high-aggression participants rated their AMs less positively under OT, compared to placebo. Although we expected these results to be more uniform across rating- and cue-types, the general pattern summarized here is consistent with our proposed model. That is, that OT administration would minimize the AM biases of high-aggression participants when within a social context and amplify them when in the absence of a socially supportive environment. While it remains unclear why changes to valence ratings following OT administration were restricted to neutral cues, it is possible that such cues are more readily skewed by underlying cognitive biases. That is, given that neutral cue words are ostensibly valence-free, it seems plausible that the interpretation of such words would be most heavily influenced by pre-existing biases.

Taken together, our findings expand upon our existing understanding of aggression and OT, both separately and collectively. First, we find additional evidence of cognitive biases in high-aggression individuals using, for the first time, AM retrieval patterns. In sum, such individuals struggle to recall specific positive events from their past, which is an AM pattern that is likely in keeping with their self-schemas. This retrieval pattern, together with other well-validated

attentional and interpretational biases (e.g.: Parrott et al., 2005; Wilkowski & Robinson, 2010), may contribute to continued externalizing behaviours in ways that parallel the effects of AMs within affective episodes. Second, we find additional evidence that intranasal OT administration can alter cognitions related to the self-concept. Specifically, the negative AM retrieval bias of high-aggression participants is reduced following OT administration. In fact, OT's ability to dampen the negative AM retrieval biases characteristic of aggression may be related to its capacity to heighten self-perceptions of prosocial personality traits (Cardoso et al., 2011; Colonnello & Heinrichs, 2014). Such parallel changes in AM retrieval and self-schemas would be in keeping with the SMS model of AM recall. Lastly, we found that the effects of OT administration on AM retrieval were subject to contextual and individual factors. Namely, overgeneral AM retrieval was reduced exclusively in high-aggression participants and uniquely within the social condition. This may reflect a greater sensitivity to exogenous OT for high-aggression individuals, perhaps as a consequence of reduced levels of endogenous OT. Although no study to date has investigated the relation between endogenous OT and aggressive behaviour in humans, parallel investigations have suggested a negative association between these variables. For instance, lower levels of endogenous OT have been associated with callousness and conduct problems in humans (Levy et al., 2015), as well as heightened aggression in dogs (MacLean et al., 2017) and horses (Lee & Yoon, 2021). As such, OT administration may normalize otherwise deficient OT levels in aggressive individuals, producing greater parity with their low-aggression peers. This, in turn, could diminish the cognitive biases otherwise seen in aggressive individuals.

Notably, this individual difference effect was also mediated by contextual factors, producing clearly reduced AM biases within a social context in contrast to seemingly worsened biases in a non-social environment. This may reflect OT's ability to facilitate the processing of

positive social information (Simplicio et al., 2008). That is, the positive aspects of the social interaction during the social condition were amplified by OT, thereby undermining the interpretational biases normally seen in high-aggression individuals. In the absence of any social information, these biases were instead unchanged, and in some instances amplified. This interpretation would be consistent with prior research showing that OT administration facilitates prosocial behaviour in a social context but impedes prosocial behaviour in a non-social context (Declerck et al., 2010).

There are a number of limitations in this project that warrant discussion. First, as much of the recent work on AM retrieval, this project focused primarily on memory specificity and did not examine the content of retrieved events. A more thorough evaluation of the nature of retrieved AMs (e.g.: affiliative vs. agonistic; social vs non-social) could provide additional insights into the retrieval biases of high-aggression individuals. Future projects could include qualitative ratings of the content of the AM recollections, which may be used to further support or disconfirm the tenets of the SMS model and prove critical in formulating a unified model of overgeneral AM. Relatedly, limiting the valence ratings of AM recollections to only positive and negative scales may have, in turn, limited our ability to evaluate the extent of AM retrieval biases. It could prove fruitful for future projects to expand these rating to include additional emotional categories. The addition of an "angry" or "frustrated" scale could further elucidate our understanding of AM retrieval biases in aggressive individuals. Additionally, while our data does expand our understanding of the cognitive biases of high-aggression individuals, it does not allow us to investigate how changes in AM retrieval patterns influence subsequent behaviour. More comprehensive investigations that include a behavioural component may be able to address this shortcoming in the future. Within the depression and PTSD literature, the contributory nature of overgeneral AM to symptomatology

over time is clear (e.g.: Gibbs & Rude, 2004; Hermans et al., 2008). A similar causal mechanism between overgeneral recall and subsequent externalizing behaviour has not yet been investigated. Although our findings contribute some theoretical support to this hypothesis, a more robust longitudinal design would be necessary to demonstrate it more conclusively. It is also worth noting that we did not specifically recruit a high-aggression sample for this study; rather, we compared higher- to lower-aggression participants within a random community sample. Consequently, only a small portion of our sample reported extreme aggression scores, which may have limited our statistical power. Future works would benefit from specifically recruiting high-aggression participants, perhaps by using more exciting or evocative wording in their advertisements. Lastly, although widely used, the intranasal administration of OT itself invites certain interpretational limitations. While there is compelling evidence that intranasal OT administration does increase the availability of OT in the brain (Martins et al., 2020; Quintana et al, 2018), this procedure also increases the availability of peripheral OT (see Leng & Ludwig, 2016 for a review). As such, it is plausible that some of our observed findings reflect peripheral effects of OT, such as changes to heart rate or blood pressure. Future works could address this shortcoming by including a peripheral administration control group, which has also been suggested elsewhere (Leng & Ludwig, 2016).

In sum, this project found that high-aggression participants produce a greater number of overgeneral AMs following positive cues when compared to lower-aggression controls. We also found that the administration of a single dose of intranasal OT could alter these facets of AM retrieval, resulting in more specific and less negatively-valenced AMs selectively within high-aggression individuals. Critically, this drug effect was exclusive to the social condition, with OT administration instead producing less positively-valenced recollections within a non-social context. This discrepancy highlights the potentially deleterious effects of OT administration in the

absence of social contact, which has been previously observed within depressed populations (Wong et al., 2021). Although the mechanism underlying these effects are not fully understood, some viable hypotheses deserve consideration. As previously mentioned, OT administration has been shown to alter self-perceptions of personality, causing participants to see themselves as more affable and sociable (Cardoso et al., 2011; Colonnello & Heinrichs, 2014). If AM retrieval is facilitated for self-schema-congruent recollections, then modifications to one's self-concept would produce parallel modifications to their AM retrieval. In addition, OT administration has also been shown to reduce a variety of cognitive biases that are characteristic of internalizing disorders (e.g.: Clark-Elford et al., 2014; Ellenbogen, 2011); our findings may reflect an extension of that work into the biases predictive of externalizing behaviour.

This work highlights the importance of constructing a comprehensive model of AM biases in aggressive individuals; if patterns of AM retrieval can be used to predict symptomatology and response to intervention in internalizing disorders, then perhaps they could provide a similar structure to externalizing behaviours. The present study replicates some of the limited findings about AM recall in high-aggression participants as well as further supporting the growing evidence for contextual effects of OT. It also demonstrates, for the first time, that the AM retrieval biases in aggressive individuals are potentially as malleable as those seen in depressed individuals. This is especially important, given the recent evidence showing that OT serves as an effective adjunct to psychotherapy, facilitating changes to cognition (Guastella et al., 2009) as well as improvements and maintenance even months following the final administration (Ellenbogen et al., 2018). If the same is true of externalizing behaviours, then this may represent the first step in a novel approach to understanding and reducing aggression and violence.

Table 1. Summary of Demographic and Self-Report Data

Demographic Data		
Sample Size	63	
Sex (% female)	51	
Age (*M* (*SD*))	24.60 (4.22)	
Self-Report Data	Mean	Standard Deviation
ASR Aggressive Behaviour	4.86	3.99

Note. ASR = Achenbach System of Empirically Based Assessment - Adult Self-Report.

Table 2. Summary of Autobiographical Memory Data by Cue Valence

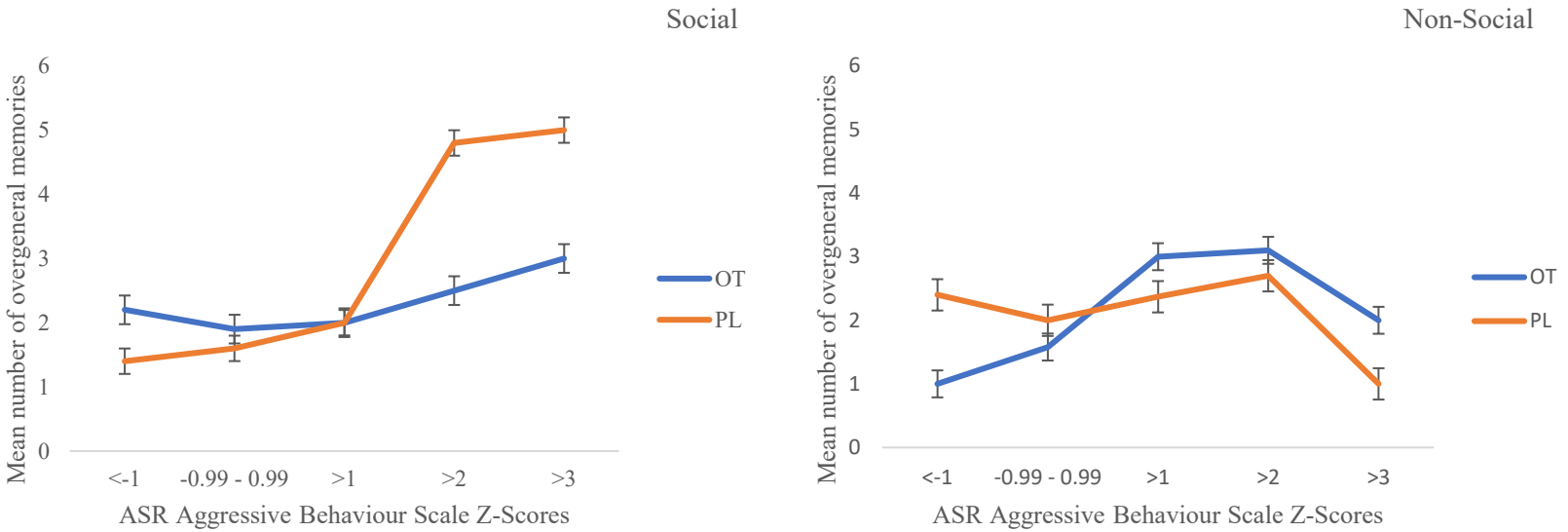
	Placebo		Oxytocin	
Cue Valence	Mean	Standard Deviation	Mean	Standard Deviation
Non-Social Condition				
All – Overgeneral Recall	6.24	3.85	6.53	3.94
All – Positive Valence	4.09	0.61	4.08	0.59
All – Negative Valence	2.69	0.67	2.69	0.61
Positive – Overgeneral Recall	2.15	2.03	1.84	1.68
Positive – Positive Valence	5.35	0.82	5.33	0.79
Positive – Negative Valence	1.78	0.60	1.65	0.56
Negative – Overgeneral Recall	2.72	1.76	2.98	1.71
Negative – Positive Valence	2.31	0.75	2.29	0.68
Negative – Negative Valence	4.28	1.15	4.35	1.04
Neutral – Overgeneral Recall	1.34	1.28	1.73	1.54
Neutral – Positive Valence	4.59	0.91	4.61	0.90
Neutral – Negative Valence	2.04	0.79	2.08	0.81
Social Condition				
All – Overgeneral Recall	6.57	3.76	6.41	3.70
All – Positive Valence	4.16	0.64	4.09	0.59
All – Negative Valence	2.60	0.58	2.59	0.62
Positive – Overgeneral Recall	1.83	1.55	2.00	1.75
Positive – Positive Valence	5.36	0.88	5.27	0.84
Positive – Negative Valence	1.62	0.53	1.58	0.51
Negative – Overgeneral Recall	3.14	1.86	2.98	1.90
Negative – Positive Valence	2.47	0.71	2.44	0.71
Negative – Negative Valence	4.20	1.03	4.14	1.13
Neutral – Overgeneral Recall	1.57	1.42	1.40	1.27
Neutral – Positive Valence	4.66	0.96	4.55	0.91
Neutral – Negative Valence	1.99	0.69	2.04	0.78

Table 3. Summary of Regression Analyses

Cue Valence	SE	R^2	B	LLCI	ULCI	p
Non-Social Condition						
All – Overgeneral Recall	0.128	0.036	0.193	-0.063	0.449	0.136
All – Positive Valence	0.015	0.067	-0.031	-0.061	-0.001	0.041
All – Negative Valence	0.017	0.010	0.014	-0.021	0.049	0.428
Positive – Overgeneral Recall	0.065	0.035	0.097	-0.034	0.228	0.143
Positive – Positive Valence	0.018	0.002	-0.006	-0.042	0.029	0.724
Positive – Negative Valence	0.019	0.002	0.007	-0.031	0.044	0.714
Negative – Overgeneral Recall	0.067	0.002	0.023	-0.111	0.158	0.732
Negative – Positive Valence	0.026	0.017	-0.027	-0.081	0.026	0.306
Negative – Negative Valence	0.037	0.001	0.006	-0.067	0.080	0.863
Neutral – Overgeneral Recall	0.052	0.035	0.078	-0.027	0.184	0.142
Neutral – Positive Valence	0.253	0.082	-0.059	-0.109	-0.008	0.023
Neutral – Negative Valence	0.238	0.018	0.025	-0.022	0.073	0.291
Social Condition						
All – Overgeneral Recall	0.118	0.005	-0.068	-0.030	0.166	0.561
All – Positive Valence	0.017	0.003	-0.008	-0.0431	0.0267	0.639
All – Negative Valence	0.017	0.076	-0.039	-0.074	-0.004	0.029
Positive – Overgeneral Recall	0.060	0.088	-0.146	-0.267	-0.025	0.018
Positive – Positive Valence	0.023	0.004	-0.003	-0.049	0.042	0.877
Positive – Negative Valence	0.015	0.053	-0.027	-0.058	0.002	0.069
Negative – Overgeneral Recall	0.069	0.004	0.036	-0.101	0.175	0.595
Negative – Positive Valence	0.023	0.014	-0.022	-0.070	0.024	0.345
Negative – Negative Valence	0.031	0.016	-0.032	-0.095	0.031	0.316
Neutral – Overgeneral Recall	0.053	0.016	0.052	-0.053	0.158	0.325
Neutral – Positive Valence	0.029	0.000	0.001	-0.058	0.059	0.971
Neutral – Negative Valence	0.026	0.069	-0.056	-0.109	-0.003	0.039

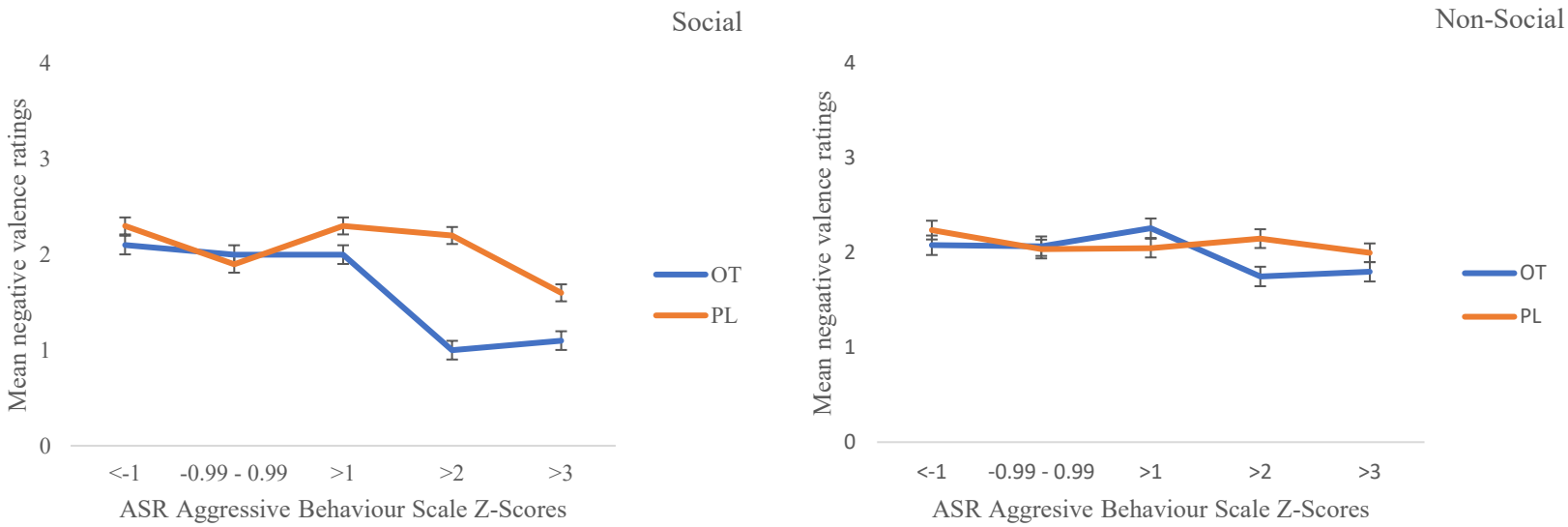
Note. LLCI = Lower Limit 95% Confidence Interval, ULCI = Upper Limit 95% Confidence Interval

Figure 1. Moderation of Overgeneral Recall for Positive Cues



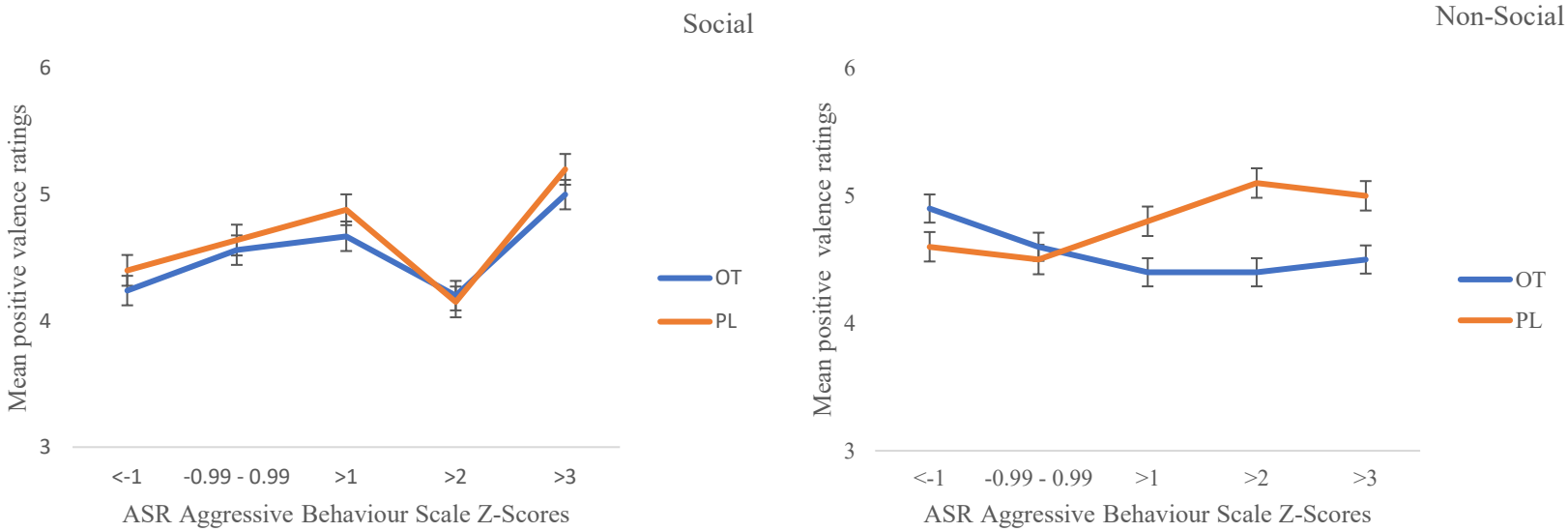
Note. These graphs represent reduced overgeneral recall following oxytocin administration selectively in those with elevated self-reported aggression, exclusively in the social (left side) condition. Results are separated by sample-specific z-scores. Error bars represent standard errors; OT = oxytocin, PL = placebo, ASR = Achenbach System of Empirically Based Assessment - Adult Self-Report.

Figure 2. Moderation of Negative Valence Ratings for Neutral Cues



Note. These graphs represent lowered negative-valence ratings following oxytocin administration selectively in those with elevated self-reported aggression, exclusively in the social (left side) condition. Higher ratings represent increased negative valence. Results are separated by sample-specific z-scores. Error bars represent standard errors; OT = oxytocin, PL = placebo, ASR = Achenbach System of Empirically Based Assessment - Adult Self-Report.

Figure 3. Moderation of Positive Valence Ratings for Neutral Cues



Note. These graphs represent lowered positive-valence ratings following oxytocin administration selectively in those with elevated self-reported aggression, exclusively in the non-social (right side) condition. Higher ratings represent increased positive valence. Results are separated by sample-specific z-scores. Error bars represent standard errors; OT = oxytocin, PL = placebo, ASR = Achenbach System of Empirically Based Assessment - Adult Self-Report.

Chapter 4: General Discussion

The purpose of this work was to investigate the relation between the nonapeptide OT and aggressive behaviour. To this end, we completed two projects examining this association across distinct populations and methodologies. Study 1 was a meta-analysis of animal models in which the availability of endogenous OT was genetically manipulated, and subsequent aggressive behaviour was observed in semi-naturalistic settings. In brief, we found that reductions in OT availability were associated with heightened aggressive behaviour in male mice, but that the nature of this relation was subject to important developmental, individual, and contextual considerations. Study 2 aimed to explore the effects of exogenous OT administration on human aggression, by investigating the effects of OT on AM biases that may contribute to externalizing behaviours. In sum, we found that OT administration leads high-aggression individuals to recall fewer overgeneral autobiographical events in response to positive cue words and to rate the emotional valence of their neutrally-cued recollections less negatively when within a social context.

Study 1: Genetic Manipulations of the OT System and Subsequent Aggression

More specifically, in Study 1 we found that changes in aggressive behaviour were contingent on the type of genetic manipulation performed. Our results suggest that the in-utero absence of OT exposure was the defining feature of heightened aggression in adulthood, at least in male mice. That is, methodologies that eliminate both fetal and postnatal OT exposure consistently produced increased adulthood aggression. In contrast, procedures that only eliminate postnatal exposure to OT were not associated with statistically significant changes in aggressive behaviour. Although additional distinctions exist between these methodological approaches, alterations to fetal OT exposure seem to be the most prominent and meaningful discrepancy, at least in terms of subsequent aggression (Dhakar et al., 2012). This effect was consistent across

different behavioural paradigms and experimental designs. Moreover, this effect persisted in the single study that accounted for levels of maternal involvement and care (Takayanagi et al., 2005). We also found, albeit across only a small number of studies, that disruptions to OT production or binding were associated with proportionally greater increases to intrastrain aggression, relative to interstrain, aggression. This finding is notable, given that previous research suggests that intrastrain aggression is typically dampened when compared to interstrain aggression in genetically unmodified mice (Hattori et al., 2015). Additionally, this finding is of particular theoretical importance as it suggests that OT plays a central role in the maintenance of normative in-group biases. This is in keeping with more recent findings within the human literature that suggest that OT selectively increases parochial altruism (e.g.: De Dreu et al., 2012; Zhang et al., 2019). Lastly, our results suggest that the behavioural paradigm that elicits a territorial challenge was most consistently associated with heightened aggression in OT deficient mice. The paradigm that elicits a resource-access challenge was associated with the greatest overall increase in aggressive behaviour; however, this approach was used only once, limiting the generalizability of this finding. Importantly, the developmental timing of OT deficiency was the most critical variable in determining adulthood aggression, as findings involving in-utero OT deficits were most consistent. Approaches producing post-partum OT deficiencies produced mixed results, perhaps suggesting a greater sensitivity to contextual factors for postnatal OT deficiencies. Taken together, these findings suggest that OT plays an important role in the development of aggressive behaviour in mice, with differential effects across developmental stages.

Potential Mechanisms

Although the results of the meta-analysis add to a growing body of literature that implicates the OT system in aggressive behaviour, the mechanisms through which OT deficiencies contribute

to subsequent aggression remain poorly understood. Nevertheless, some viable hypotheses merit consideration. In particular, there is evidence from animal-model studies that a single perinatal exposure to OT or OT antagonists can produce robust behavioural changes that emerge weeks or even months later (see Miller & Caldwell, 2015 for a review). For instance, female mice exposed to an OT antagonist within 24 hours of birth show reduced social approach behaviours at 15 weeks of age, when compared to control animals (Mogi et al., 2014). Long term behavioural changes following perinatal OT manipulations have also been observed for parental behaviours (Bales et al., 2007; Mogi et al., 2014) and sexual behaviours (Cushing et al., 2005; Perry et al., 2009). Given the enduring nature of these behavioural changes, it has been suggested that OT plays a role in neural development, contributing to brain organization, cell morphology, or receptor sensitivity (Carter, 2003; Miller & Caldwell, 2015).

While studies addressing such developmental questions directly are limited, some congruent findings that may be pertinent within the context of aggression have been reported. For example, female prairie voles exposed to exogenous OT within 24 hours of birth demonstrate increased estrogen receptor expression at three weeks of age, when compared to control animals (Yamamoto et al., 2006); the same study also found that both male and female voles showed reduced estrogen receptor expression when exposed to an OT antagonist within 24 hours of birth. In pigs, exogenous OT administration at one, two, and three days of age was associated with greater hormonal stress reactivity at 8 weeks of age and with reduced sensitivity to a pharmacological intervention that reduces cortisol concentrations at 11 weeks of age (Rault et al., 2013); in turn, these animals were also found to be more aggressive when compared to control conspecifics. Together, these findings suggest that perinatal exposure to elevated levels of OT produces long-term dysregulation of the stress response, likely by acting on the hypothalamic-

pituitary-adrenal (HPA) axis. As such, atypically high or low levels of perinatal OT can result in long lasting neural changes, with parallel alterations to behaviour. It is plausible that such effects of perinatal OT could be extended to prenatal development as well, with fetal OT exposure potentially impacting neural development in kind. To our knowledge, no studies to date have directly investigated the effects of prenatal OT on subsequent brain structure or functioning. Nevertheless, previous investigations have found that fetal OT exposure is associated with lifespan behavioural changes (e.g.: Winslow & Insel, 2002), including several of the research articles reviewed in the meta-analysis. It stands to reason that such behavioural modifications would be predicated on underlying neural or hormonal changes. As such, we posit that the association between fetal OT deficiencies and adulthood aggression is secondary to the relation between fetal OT exposure and brain development.

Based on the findings reviewed above, certain neurodevelopmental underpinnings seem especially plausible. First, if elevated perinatal OT exposure results in subsequent HPA axis overactivity (Rault et al., 2013), then perhaps early-life OT deficiencies instead produce a blunted stress response in adulthood. Importantly, a recent review article found that the relation between HPA axis activity and animal aggression follows a U-shaped pattern, with both hypo- and hyperactivity of the stress response being associated with increased aggression (Walker et al., 2018). As such, it is plausible that fetal OT deficiencies results in HPA axis hypoactivity which, in turn, results in elevated aggression. Second, if the absence of perinatal OT, achieved via OT antagonists, produces reduced estrogen receptor expression (Yamamoto et al., 2006), then perhaps prenatal OT deficiency produces parallel decreases in estrogen receptor genesis. While many studies investigating the association between estrogen and aggression have suggested a positive relationship (see Trainor et al., 2006 for a review), the nature of this relation remains unclear.

Specifically, other studies have found important moderation by additional variables such as sex (Clipperton-Allen et al., 2011), age (Kawai et al., 2003; Nomura et al., 2002), and duration of day-night cycles (Trainor et al., 2007; Trainor et al., 2008), with increased estrogen availability being associated with both elevated and reduced aggression according to environmental and individual differences. To illustrate, the administration of estrogen receptor agonists has been found to increase aggression in mice housed under short days with only eight hours of light, but to instead decrease aggression in mice housed under long days with 16 hours of light (Trainor et al., 2007). Within this inconsistent literature base, evidence of decreased aggression following estrogen exposure has been reported in both animals (Colman et al., 2009; Filby et al., 2011) and humans (Kyomen et al., 1999; Shelton & Brooks, 1999). Although the current state of the literature makes it difficult to draw unambiguous interpretations, it is plausible that decreased estrogen binding is a contributing factor to the heightened aggression seen in some OT knockout mice. More importantly, decreased estrogen binding may be impacting subsequent aggression indirectly through its relationship with serotonin. Estrogen plays a crucial role in the serotonergic system, primarily by stimulating serotonin synthesis and delaying serotonin degradation and reuptake (see Del Rio et al., 2018 for a review). In turn, serotonin is generally found to have a negative relationship with aggressive behaviour, although this association is not unequivocal (see Duke et al., 2013 for a meta-analysis). As such, reduced estrogen binding would result in decreased serotonin synthesis which could, in turn, contribute to elevated levels of aggression.

Relatedly, an association between pre- and perinatal OT deficiency and decreased adulthood social approach behaviours has been shown (e.g.: Lazzari et al., 2013; Mogi et al., 2014). While the specific mechanisms contributing to these behavioural changes are not yet known, some potentially relevant brain regions and neural circuits have been suggested (see Steinman et al.,

2019 for a review). Nevertheless, it is possible that the reduced social motivation seen in OT deficient animals is contributing to heightened aggression by making all social encounters less pleasant and more agonistic. As a final consideration, it is also likely that interactions between these structures and systems are central determinants of aggressive behaviour, which may account for some of the individual and contextual variability summarized above. While our interpretations are based on theoretical extensions of previous findings, empirical data supporting or refuting these hypotheses are still unavailable. Ultimately, research projects addressing these hypotheses directly, as well as their potential interactions, would be needed to draw more definitive conclusions about the relation between prenatal OT and lifespan aggression. Nonetheless, we contend that the above-mentioned mechanisms are viable targets for future works. In sum, while the underlying mechanisms remain obscured, the association between fetal OT deficiency and adulthood aggression in mice is strongly supported by our meta-analysis.

Study 2: Intranasal OT and AM Retrieval Biases

While it is plausible that endogenous OT plays a similar developmental role in other species, human behaviour is more heavily influenced by higher-order top-down cognitive processes. For this reason, Study 2 examined the effects of OT administration on a particular form cognitive bias that may contribute to externalizing behaviours. Namely, we investigated the relation between exogenous OT and the specificity and emotional valence of AMs. We found that high-aggression participants struggled to recall specific autobiographical events in response to positive cue words, in keeping with previous investigations using incarcerated samples (Neves & Pinho, 2015; Neves & Pinho, 2018). This finding is consistent with the proposals of the Self Memory System, in which AMs consistent with one's self-concept are most easily retrieved; as such, aggressive individuals may have difficulty retrieving specific positive episodes from their

past as such recollection may be inconsistent with their self-schemas. We also found that the administration of exogenous OT selectively altered patterns of AM retrieval in high-aggression participants, resulting in the increased retrieval of specific and less negative events. Importantly, this effect was exclusive to the social condition, with OT administration instead producing amplified negative AM retrieval biases in a non-social context. Taken together, these findings suggest that OT's effects on self-referential processes are subject to important moderation by both individual and contextual factors. More broadly, they suggest that OT administration, within a social environment, can facilitate the retrieval of less negative AMs in individuals otherwise prone to negative retrieval biases. This, in turn, could alter self-perceptions congruently, leading to a more sociable and affable view of the self. Conversely, when administered in a non-social environment, OT seems to amplify existing AM biases, which could, in turn, lead to more hostile self-perceptions. Parallel results have also been found within the context of depressive symptoms, with negative AM retrieval biases being selectively amplified for high-depression participants exclusively in a non-social context (Wong et al., 2021). Interestingly, these effects on self-referential processes are in keeping with, and perhaps even contributing to, a nuanced understanding of OT's effects on prosocial behaviour. That is, just as OT administration can promote trust and generosity in positive or neutral social environments (e.g.: Baumgartner et al., 2008; Kosfeld et al., 2005), it can also diminish negative AM retrieval biases when in a social context. Likewise, just as OT administration can instead increase aggression and deception in a competitive environment (e.g.: De Dreu et al., 2012; Shalvi & De Dreu, 2014), it can also amplify those same AM biases in a non-social context.

Potential Mechanisms

While the exact mechanisms underlying these individual and contextual differences are not yet fully understood, some viable models have been proposed. Perhaps most compelling is the Social Salience Hypothesis (SSH), which stipulates that OT increases the salience of social cues in one's environment (see Shamay-Tsoory & Abu-Akel, 2016 for a review). Briefly, this model suggests that OT, through its interactions with the dopaminergic system, increases attention towards both positive and negative social information. In turn, this would amplify the emotional context of one's social environment and contribute to OT's highly context-sensitive effects. In support of this model, OT administration has been found to increase attention, measured via eye-gaze, towards socially relevant information in both primates (Dal Monte et al., 2014) and humans (Domes et al., 2013; Tollennar et al., 2013). Further, these effects have been found to be equivalent for both positive and negative social stimuli (e.g.: Le et al., 2020b; Tollennar et al., 2013), although selective eye-gaze for specific stimuli valences has also been reported (e.g: Domes et al., 2012). Interestingly, OT administration has also been found to increase self-ratings of vividness for AMs recalled within a social context (Wong et al., 2021), suggesting that OT may also amplify social salience within recollections for past events. Importantly, the SSH also stipulates that the interpretation of and response to social cues will be dependent on individual differences, with biological, psychological, and personality factors contributing to inter-individual variability. Taken together, a heightened awareness of contextual cues would amplify baseline cognitive and social biases, resulting in both context- and individual-based effects. This is in keeping with the considerable inconsistency within the OT literature and could explain the diametrically opposed attentional changes sometimes seen following OT administration (e.g.: Kim et al., 2014 vs. Leslie et al., 2020).

Critically, the SSH also recognizes an additional source of individual variability. Namely, that manipulations of the OT system could have differential effects on the social cognitions and biases of different populations. That is, OT administration may amplify cognitive biases in certain individuals by increasing their awareness of the social cues that trigger them. For others, OT may instead minimize cognitive biases, most likely by dampening the neural responses of brain regions associated with threat processing (e.g: Bertsch et al., 2013b). In fact, a growing body of literature suggests that OT may alleviate cognitive biases specifically in vulnerable populations. For instance, OT has been found to selectively diminish negative self-appraisals in high-anxiety participants (Alvares et al., 2012). Likewise, OT has also been shown to selectively improve the empathic accuracy of men with high autism quotients (Bartz et al., 2010b; Bartz et al., 2019) and the theory of mind abilities of men with low empathy quotients (Feeser et al., 2015). Further, OT has been found to reduce the attentional bias towards negative social stimuli in women with borderline personality disorder (Bertsch et al., 2013b) and participants with elevated depressive symptoms (Domes et al., 2016; Ellenbogen et al., 2011), psychiatric disorders typically characterized by hypervigilance for negative stimuli. While the mechanism underlying these selective effects in vulnerable individuals are not yet fully understood, it has been suggested that this is a reflection of OT saturation (Shamay-Tsoory & Abu-Akel, 2016). That is, individuals at risk for social dysfunctions and biases may by experiencing such difficulties, in part, due to a lack of endogenous OT. As such, the administration of exogenous OT corrects these biases by increasing OT availability. In contrast, healthy controls would already experience normative levels of endogenous OT, creating a ceiling effect in which exogenous OT produces no clinically meaningful changes, at least in terms of cognitive biases.

This interplay between heightened social salience and individual factors could explain the context-specific nature of the OT literature, as well as the selective nature of our findings. That is, under placebo, baseline cognitive biases in high-aggression individuals could result in an unfavorable interpretation of the neutral social context. In turn, this sense of potential social threat may activate self-schemas related to interpersonal conflict, resulting in selective difficulties retrieving positive AMs. Under OT, these biases may be reduced, allowing for the neutral social context to be interpreted more positively, resulting in diminished negative self-schema related AM retrieval. Finally, when in a non-social context, the lack of social cues reduces OT's effectiveness, thereby maintaining and even amplifying underlying cognitive biases. Again, this is in keeping with previous findings that OT worsens negative AM retrieval biases in individual with elevated depressive symptoms, uniquely in a non-social context (Wong et al., 2021).

An Integrated Conceptualization

Taken together, the results of our studies suggest that OT may alter the frequency of aggressive behaviour by influencing underlying cognitive biases about both the self (AM retrieval biases) and others (in-group biases). These effects are, like much of the OT literature, contingent on individual and contextual factors, with OT administration being associated with a selective reduction in AM retrieval biases in high-aggression participants, uniquely within a social context. Additionally, we find that developmental factors relating to early-life OT availability are also important moderators of the relation between OT and aggression. Namely, that fetal OT deficiency is consistently and reliably associated with elevated levels of adulthood aggression in mice. This suggests that OT may also act on biological determinants of aggression, by contributing to early-life brain development and organization. In sum, we find that deficiencies in prenatal OT are associated with increased aggression and that elevating levels of OT via intranasal administration

is associated with changes in cognition that are consistent with putative reductions to externalizing behaviours. Together, these findings suggest that low levels of OT are associated with the potential risk of aggressive behaviour throughout the lifespan.

However, such a straightforward interpretation is unlikely. Specifically, if increased OT availability in adulthood results in diminished cognitive biases related to aggressive behaviours in humans, then why do adult mice with post-natal OT deficiencies not show increased aggression? While a clear answer to this question is not yet available, we suggest that OT plays a different role in aggression at different points of development. It is plausible that fetal and perinatal OT contributes to biological determinants of aggression, which are important across species. Conversely, lifespan OT may instead play a more prominent role in cognitive determinants of aggression, which would be most significant in humans. It also should not be understated that direct translations of animal data to human models will be lacking, given the significant cognitive and social differences between humans and non-human animals. Relatedly, it is also plausible that biological differences between species, such as volume of OT receptor expression or degree of OT sensitivity, are contributing to this discrepancy. As such, a more plausible interpretation is that OT's effects on aggression vary according to developmental stage and across species.

Importantly, an additional discrepancy between our findings and previously published results remains unexplained. Namely, previous works have found that OT administration can heighten antagonistic and aggressive behaviours, at least in certain contexts (e.g.: De Dreu et al., 2012; Shalvi & De Dreu, 2014). In contrast, our findings suggest that reduced OT availability represents a risk for aggressive behaviour. We suggest that this discrepancy reflects difference in baseline OT availability. Previous research has found that endogenous OT availability is negatively associated with callous-unemotional traits (Dadds et al., 2013b; Levy et al., 2015) and

conduct disorder (Bakker-Huvenaars et al., 2020) in children. As such, and in keeping with our findings, low levels of endogenous OT may be associated with subsequent risk of aggression. For such individuals, the administration of exogenous OT may normalize OT availability, resulting in a reduced risk for aggression. Conversely, healthy controls, who presumably experience typical levels of OT availability, may experience a greater risk for aggression when OT levels are elevated following exogenous administration. Put simply, the relation between OT and aggression may follow a continuum, with both unusually low and high levels of OT availability increasing the risk for aggressive behaviour.

Concluding Remarks

While many questions regarding the relation between OT and aggression remain, our findings suggest that OT's effects on aggressive behaviour are dependent on developmental, contextual, and individual factors. While atypically low levels of OT seem to contribute to developmental and cognitive determinants of aggression, important individual and contextual variability persists. Additionally, atypically high levels of OT may also contribute to aggression through different mechanism, most likely by amplifying in-group biases. Most importantly, it is likely that the OT system interacts with additional neural circuits and hormones in ways that are beyond the scope of this project. Ultimately, a comprehensive evaluation of OT's interactions with individual, contextual, and biological factors will be needed to achieve a complete understanding of this relationship. Further, we suggest that future works investigating the relation between OT and aggression consider baseline endogenous OT availability as a key moderator. Nevertheless, we find compelling evidence that OT deficiencies can increase one's risk of aggressive behaviour.

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