Oxytocin Administration and Emotion-Related Startle in Psychopaths: A Yawn and Startle Study

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Psychopathy is characterized by a general antisocial lifestyle with behaviors including being selfish, manipulative, impulsive, fearless, callous, possibly domineering, and particularly lacking in empathy. Contagious yawning in our species has been strongly linked to empathy. We exposed 133 students, male and female, who completed a self-report Psychopathic Personality Inventory (Revised), to a yawning paradigm intended to induce a reactionary yawn. Further, we exposed males to an emotion-related startle paradigm meant to assess peripheral amygdalar reactivity. We found that those at or above clinical levels of the PPI-R subscale Coldheartedness were significantly less likely to yawn, $\chi 2(1, N = 123) = 7.051$, $p = .008$. Other subscales were not significant. Further, we found that difference scores in peak amplitudes between Negative and Neutral stimuli in the startle paradigm were predictive of frequency of yawning ($\beta = -.383$, $p = .007$). These data suggest that psychopathic traits may be strongly related to the empathic nature of contagious yawning in our species.

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A Yawn and Startle Study

by

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CHAPTER ONE

Introduction

Oxytocin

Oxytocin (OT) is primarily synthesized in magnocelluar neurons of the hypothalamic paraventricular and supraoptic nuclei, where it is then transferred (via neurophysin) to the neurohypophysis (Lim & Young, 2006; Gimpl & Fahrenholz, 2001). The OT receptor is a class-one G-protein-coupled receptor and requires cholesterol and Mg^{2+} in order to achieve a high-affinity state (Gimpl & Fahrenholz, 2001). OT and its homologues are prolific in vertebrates, but are found even in mollusks. In mammals, and in context, humans, it plays several roles in the body from a large role in reproduction, including milk let down and maternal bonding (Carter, Pournajafi-Nazarloo, Kramer, Ziegler, White-Traut, Bello, & Schwertz, 2007; Feldman, Gordon, Schneiderman, Weisman, Zagoory-Sharon, 2010) to social relationships (Heinrichs, von Dawans, & Domes, 2009). It also has a prominent role in the spectrum of sexual activity and function, osteoporosis, stress, cancer, and diabetes (Viero, Shibuya, Kitamura, Verkhratsky, Fujihara, Katoh, Ueta, Zingg, Chvatal, Sykova, & Dayanithi, 2010).

In terms of social relationships, little is known about the precise role of OT and how it works to actually build our social bonds with one another, but the literature is widening (Bora, Yucel, & Allen, 2009; Carter, 2007a; Bartz & Hollander, 2006); however, the literature on the prosocial effects of oxytocin is not lacking. OT plays a role in “mind-reading” or inferring the mental states of others from subtle facial expressions

(Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), which is certainly vital to social interactions. Exogenous administration of OT increases trust in humans while involved in a "trust game" (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Interestingly, women with elevated mean peripheral OT reactivity showed an increase in post-conflict anxiety and decreased levels of forgiveness (Tabak, McCullough, Szeto, Mendez, & McCabe, 2011), which may suggest that those who are "more attatched" or empathetic with their partner show a greater amount of anxiety when a conflict is perceived to threaten the relationship. We, as mammals, utilize this neuropeptide to the extent that it is released with just a warm touch from another (Holt-Lunstad, Birmingham, & Light, 2008).

Much of what we know about the interpersonal effects OT comes from studies where it is administered intranasally (typically between 24-40IU). Exogenous OT tends to increase prosocial behavior and has consistently shown to interact with the amygdala, a brain structure involved in fear processing and learning (Phelps, 2006). For example, OT attenuated the affective rating of aversively conditioned faces (Petrovic, Kalisch, Singer, & Dolan, 2008) and Domes, et al. (2007) showed reduced right-side amygdala responses to emotional faces, suggesting that a general decrease in amygdalar activity decreases general arousal, anxiety, and fear reactivity, and thereby promotes prosocial behavior. Similarly, intranasal OT has been shown to increase the ability of subjects to recognize the emotion of fear (Fisher-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010), though in this particular study other emotions were left unaffected.

Clearly OT has influence on the amygdala, though its role is paradoxical. In many studies, there is evidence of a suppression of amygdalar activity reactivity while it

increases sensitivity to amygdala-related emotions (Labuschagne, Phan, Wood, Angstadt, Chua, Heinrichs, Stout, & Nathan, 2010; Fisher-Shofty, et al., 2010). Gamer, Zurowski, & Büchel (2010) suggest that OT modulates specific subregions of the amygdala and, depending on the emotional valence of a face, may increase or decrease activation in specific subregions of the human amygdala. What's more, is that OT has been shown to increase envy and Schadenfreude (gloating over other's misfortune) when administered intranasally (Shamay-Tsoory, Fischer, Dvash, Haari, Perach-Bloom, & Levkovitz, 2009). In this case, exogenous OT is, perhaps, amplifying the emotional prescription to an antisocial behavior, and not actually promoting antisocial behavior directly. Unfortunately, the research is still unclear about how exactly this phenomena and other prosocial phenomena occur in the presence of manipulated OT levels. It is usually the case, however, that OT studies are in the context of prosocial behavior and OT may be biased towards this end. However, it is clear from Shamay-Tsoory et al. (2009) that OT may have a role in antisocial behavior, but its locus is certainly unclear.

Oxytocin has other personal and prosocial benefits. It is well known that OT has anxiolytic properties (Gamer & Buchel, 2012; Ditzen, Schaer, Gabriel, Bodenmann, Ehlert, Heinrichs, 2009; Ayers, Missig, Schulkin, & Rosen, 2011) in part by reducing functional connectivity between the amygdala and brainstem regions implicated in autonomic manifestations of emotional experience (Kirsch, Esslinger, Chen, Mier, Lis, Siddhanti, Gruppe, Mattay, Gallhofer, & Meyer-Lindenberg, 2005). It has also been shown to reduce subjective arousal ratings for threatening stimuli (Norman, Cacioppo, Morris, Karelina, Malarkey, DeVries, & Berntson, 2010). As well, OT has been shown to have amnesic properties. Heinrichs, Meinlschmidt, Wippich, Ehlert, and Hellhammer

(2004) showed that intranasal oxytocin administration selectively influences memory performance depending on the kind of memory and psychobiological relevance of stimuli. Interestingly, male OT knockout mice fail to develop social memory on the habituation-dishabituation test (Winslow, Hearn, Ferguson, Young, Metzuk, & Insel, 2000). In fact, OT knockout mice show an array of social memory deficits (reviewed in Lee, Macbeth, Pagani, & Young, 2009). Others have shown similar results, that oxytocin can impair memory for social and non-social objects (Herzman, Young, Bird, & Curran, 2012). Lee et al. (2009) review learning and memory in rat models, which show consistent results next to human models of altered memory function due to oxytocin administration.

While this discussion of oxytocin is focused on interpersonal behavior, it is most certainly involved in a wide range of sexual behaviors and functions. Many of its uses in females have been discussed (White-Traut et al., 2009), but there is also an established body of literature surrounding oxytocin's importance in male sexual function, particularly in rat models, but also in humans (Thackare, Nicholson, & Whittington, 2006; Succu, Sanna, Cocco, Melis, Boi, Ferry, Argiolas, & Melis, 2008). There is even a case report where a male with anorgasmia was successfully treated with intranasal oxytocin spray (IsHak, Berman, & Peters, 2007). What's most impressive is that the male in the case study was treated at 82 years of age, suggesting OT is important across the lifespan and also that production may decrease with old age. Consistent findings have been found in females, where plasma OT was significantly correlated with levels of arousal and vaginal lubrication (Salonia, Nappi, Pontillo, Daverio, Smeraldi, Briganti, Fabbri, Zanni, Rigatti, & Montorsi, 2005). The literature concerning oxytocin's role in sexual function is

established and growing; Lee et al. (2009) discusses in depth OT's role in sexual function in rats as well as, briefly, in humans.

Psychopathy

Psychopathy is characterized by a general antisocial lifestyle including being selfish, manipulative, impulsive, fearless, callous, domineering, and particularly lacking in empathy (Hare, 2003; Weber, Habel, Amunts, Schneider, 2008). The disorder is typically assessed via the Psychopathic Check List-Revised (PCL-R) developed by Hare (2003) or the Psychopathic Personality Inventory (PPI-R) developed by Lilienfeld and Widows (2005). Each measure operationalizes two discrete components within psychopathy: a primary (affective) and secondary (behavioral) components (Levenson, Kiehl, Fitzpatrick, 1995; Hare 2003, Lilienfeld & Widows, 2005), where primary encompasses features including cruelty and lack of affect and secondary encompasses features such as impulsivity and aggression. Psychopathy and its close relative Antisocial Personality Disorder (ASPD) are found overwhelmingly in males (Cale & Lillienfeld, 2002). Additionally, psychopathy carries specific brain abnormalities including structural and functional impairments of the orbitofrontal-ventromedial prefrontal cortex as well as the amygdala (Gao, Glenn, Schug, Yang, Rain, 2009; Weber et al., 2008). Psychopaths demonstrate an overall small but marked decrease in the ability to recognize emotion in others (Wilson, Juodis, & Porter, 2011; Kosson, Suchy, Mayer, & Libby, 2002), which is also associated with decreased amygdalar function, particularly with fearful faces (Jones, Laurens, Herba, Barker, & Viding, 2009). Further, Wilson and colleagues (2011) found that psychopaths demonstrated a greater deficit in emotional processing when a particular task involved a verbal response. Kosson et al. (2002) showed a slight overall decreased

ability to recognize emotion, but a large deficit in recognizing disgust in others when the task involved non-verbal responses. It has also been shown that psychopaths fail to exhibit a conditioned response to aversive Pavlovian conditioning (Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002), which suggests deficiencies in limbic-subcortical and cortical structures. Other deficiencies in limbic and paralimbic structures have also been found (Ermer, Cope, Nyalakanti, Calhoun, Kiehl, 2012).

Over the years, psychopathy has been teased away from related disorders such as Conduct Disorder (CD) and Antisocial Personality Disorder (APD) (Abramowitz, Kosson, Seidenberg, 2004; Rogstad & Rogers, 2008). What sets psychopathy apart from its close relatives is its distinct emotional profile. That is, psychopathy involves a prevalent emotional profile consisting of a considerable reduction in empathy as well as a predictable behavioral profile of criminal activity and, generally, violence (Frick, O'Brien, Wootton, & McBurnett, 1994). Interestingly, those with psychopathy employ instrumental aggression more than reactive aggression (Frick, Cornell, Barry, Bodin, & Dane, 2003; Cornell, Warren, Hawk, Stafford, Oram, & Pine, 1996), though both types of aggression are certainly present in antisocial behavior (Blair, 2004). Reactive aggression (sometimes listed as affective or impulsive aggression) is defined by an aggressive act frequently paired with anger that is triggered by a threatening or frustrating event, where instrumental aggression (sometimes listed as proactive aggression) is both goal oriented and contains purpose (Barratt, Stanford, Dowdy, Liebman, & Kent, 1999; Frick et al., 2003; Blair, 2004). Typical instrumental aggression may include behaviors such as conning (Forouzan & Cooke, 2005) or gaining a victim's possessions (Blair, Peschardt,

Budhani, Mitchell, & Pine, 2006). Though psychopaths demonstrate both reactive and instrumental aggression, they show greatly elevated levels of instrumental aggression.

Interestingly, there seems to be a very close relationship between psychopathy and eye contact (Dadds, Jambrak, Pasalich, Hawes, & Brennan, 2011; Dadds, Perry, Hawes, Merz, Riddell, Haines, Solak, & Abeygunawardane, 2006). Dadds and colleagues (2008) tested whether psychopathic traits are associated with decreased attention to the eye region of other's faces. They showed that adolescent males with high psychopathic traits were significantly less proficient at fear recognition as well as showed decreased eye fixations, gaze duration and frequency. Dadds et al. (2006) showed that though psychopathic children had a deficit in recognizing fear in faces, the deficit was temporarily corrected when the children were instructed to focus on the eyes of other people. Notably, Dadds et al. (2011) showed that the fathers of children who scored high on callous-unemotional traits showed similar deficits, suggesting a genetic element. Further research suggest that genetic factors play a major role in the presence of psychopathy and may consistently be observed in children through adolescence by said genetic factors (Forsman, Lichtenstein, Larsson & Andershed, 2008).

Lastly, as mentioned, one trait of psychopathy is a lack of empathy (Hare, 2003). Consistent with the findings of the eye gaze literature, Seara-Cardoso, Neumann, Roiser, McCrory, and Viding (2012) found that psychopaths show weaker empathic responses to fearful faces. Psychopathy has also been found to be inversely related to the ability to perceive emotion (in both male and females) and managing emotion (only in men) (Lishner, Swim, Hong, Vitacco, 2011). Even less hopeful, research suggests that psychopaths may even feel positive emotions when looking at sad stimuli and experience

negative emotions from viewing neutral stimuli (Ali, Amorim, Chamorro-Premuzic, 2009). There is also interesting overlap between Autism Spectrum Disorder and psychopathy in terms of empathic deficits (Jones, Happé, Gilbert, Burnett, & Viding, 2010; Dadds, Hawes, Frost, Vassallo, Bunn, Hunter, & Merz, 2009; Schulte-Rüther, Greimel, Markowitsch, Kamp-Becker, Remschmidt, Fink, & Piefke, 2011), however, there is a clear understanding that the source of empathic deficits are fundamentally different as well as the expression of the lack of empathy.

Neurochemicals and Psychopathy

Unfortunately, there does not appear to be much pharmacological research done with psychopathy. There are, however, very curious neurotransmitter and neuroendocrine associations among psychopathy and antisocial behaviors. van Honk and Schutter (2006) discuss the suppressive role of cortisol on the hypothalamic-pituitary-gonadal (HPG) axis, which can inhibit the production of testosterone as well as its efficacy on target tissue (Johnson, Kamilaris, Chrousos, & Gold, 1992 as seen in van Honk & Schutter, 2006). What's more, testosterone has an inhibitory effect on the stressed induced activation of the hypothalamic-pituitary-adrenal (HPA) axis; testosterone administration, as Boissy & Bouissou (1994) have shown, decreases sensitivity for punishment. Further, testosterone has been shown to increase antisocial behavior in men, decrease generosity (Zak, Kurzban, Ahmadi, Swerdloff, Park, Efremidze, Redwine, Morgan, & Matzner, 2009), and a cortisol:testosterone ratio might be predictive of both instrumental and impulsive aggression (Montoya, Terburg, Bos, & van Honk, 2012; Terburg, Morgan, & van Honk, 2009). In fact, a ratio with high levels of testosterone to cortisol may decrease the amount communication, specifically emotional communication, between the

amygdala and orbitofrontal cortex (Glenn, Raine, Shug, Gao, & Granger, 2011) as cortisol has been found to strengthen the communication between said regions and testosterone has been shown to reduce it (Schutter & van Honk, 2005; van Wingen, Mattern, Verkes, Buitelaar, & Fernandez, 2010). These findings are consistent with the notion that psychopathy is heavily associated with a reduced sensitivity to anxiety producing behaviors as well as antisocial and impulsive behaviors. In fact, Glenn et al. (2011) illustrated an article by Stalenheim, Eriksson, von Knorring, & Wide (1998) that found the antisocial and impulsive aspects (Factor 2) of psychopathy to be positively correlated with testosterone, but not necessarily with the emotional aspects (Factor 1). Lastly, reduced cortisol levels were found in young adult male psychopathic offenders with an established history of violence (Holi, Auvinen-Lintunen, Lindberg, Tani, & Virkkunen, 2006); similarly, a study by Cima, Smeets, & Jelicic (2008) found lower average levels of cortisol (daily) in a group of psychopathic offenders.

There has also been a discussion of a link between psychopathy and serotonin. While serotonin has certainly been directly related to depression (See Carver, Johnson, & Joorman, 2008 for a comprehensive review of 5-HT function, depression, and impulsive aggression), it has also been implicated in poor behavioral control. Serotonin enhancement (via citalopram) has been shown to directly alter moral judgment and behavior by increasing a subjects' aversion towards harming others (Crockett, Clark, Hauser, & Robbins, 2010). In this study, citalopram showed marked effects on subject's moral judgment and behavior regardless of whether they showed high or low trait empathy, though those with higher trait empathy showed a stronger effect. Harmer, Rogers, Tunbridge, Cowen, & Goodwin (2003) found in this study, acute tryptophan

depletion significantly impaired female participants' ability to recognize fearful faces; however this did not extend to the male subjects. Tryptophan supplements have also been shown to increase the recognition of happy facial expression while also decreasing the recognition of disgusted facial expressions for female subjects (Murphy, Longhitano, Ayres, Cowen, & Harmer, 2006). Serotonin appears to play a role in affect-driven tasks but its precise role is unclear.

There have been made several links between conduct disorder, impulsiveness (Carver, et al., 2008; Rogers, Tunbridge, Bhagwagar, Drevets, Sahakian, & Carter, 2003), antisocial behavior (Carver et al., 2008; Dolan & Anderson, 2003) and 5-HT, though no direct link between 5-HT and psychopathy has been firmly established. In Rogers et al. (2003), acute tryptophan depletion altered the ability of subjects to inhibit reaction to previously rewarded cues, thereby increasing impulsive behavior. Dolan and Anderson (2003) found that 5-HT function did not correlate with psychopathy as a unidimentional phenomenon, but rather was negatively related to the impulsive-antisocial factor of psychopathy. It appears that abnormal and low serotonin functioning is more related to issues of impulsivity, antisocial behavior, and overall poor behavioral control but does not appear to be directly related to the emotional component that is necessary in psychopathy.

What can be taken away from this discussion is that while the research has yet to chisel out a definite hormonal and neurochemical profile of psychopathic behavior, there is an observable connection between particular neurochemicals that elucidates what psychopathy may involve. Further, it is clear that pharmacological treatment is largely limited to related disorders that have overlapping features of psychopathy. Lastly, it

appears that pharmacological research is largely targeted at the behavioral component anti-social disorders, and pharmacological research regarding the affective component of psychopathy is only peripherally discussed.

Psychopathy and Oxytocin

Research on OT has yielded little speculation on the interplay between OT and psychopathy, though its role in mental disorders in general is steadily growing (Bora, Yucel, & Allen, 2009; Bartz & Hollander, 2006). It appears that one of the most prolific use of OT in a clinical setting is with Autism Spectrum Disorder (ASD) patients (see Carter, 2007; Green & Hollander, 2010), where there is suspected dysregulation in ASD patients and a potential to correct social deficiencies with the administration of OT. Indeed, there are clear empathic deficits associated with ASD (Schulte-Rüther, et al,, 2011). There is evidence of a dysregulation of OT in depressed women (Cyranowski, Hofkens, Frank, Seltman, Cai, & Amico, 2008), suggesting that optimal OT regulation is involved in normalized mood and has implications for an alternative treatment to depression. Oxytocin was also shown to act as an antidepressant for two animal models of depression (Arletti & Bertolini, 1987). Further, it has implications for General Anxiety Disorder (GAD). Researchers have attenuated the heightened fear response (in a clinical setting) in GAD (Labuschagne, Phan, Wood, Angstadt, Chua, Heinrichs, Stout, & Nathan, 2010) by reducing heightened amygdala activity with OT. Similarly, cortisol levels were reduced in men with early prenatal separation, which increases the chances of emotional disorders in adulthood, when treated with intranasal OT (Meinlschmidt & Heim, 2007), and Simeon and colleagues (2011) showed an OT mediated decrease in stress reactivity in individuals diagnosed with Borderline Personality Disorder. It is, then,

not surprising that women who suffer from panic disorder experience a relief of symptoms during lactation (Klein, Skrobala, & Garfinkel, 1995). Lastly, Averbeck, Bobin, Evans, and Shergill (2012) showed that patients with schizophrenia were deficient in recognizing emotions and that intranasal oxytocin improved their ability to do so. It is reasonable to suspect that OT has its role in clinical settings and could be extended to anti-social disorders such as psychopathy.

However, it is still unclear, given the literature, what will be found between psychopathy and oxytocin. It is clear to see that there may be a connection between oxytocin, a neurohormone that, in part, controls for empathy and pair-bonding, and psychopathy, a disorder that is characterized by lacking such abilities. These concepts extend to the previously discussed human studies involving intranasal oxytocin (Domes et al., 2007) and the studies involving baseline oxytocin levels (Tabak et al., 2011). What is of most concern to a possible link between OT and psychopathy is that oxytocin itself attenuates amygdalar activity (Domes, Heinrichs, Glascher, Buchel, Braus, & Herpertz, 2007; Petrovic et al., 2008; Lubin, Elliot, Black, & Johns, 2003), and reduces anxiety and cortisol levels (Petrovic et al., 2008; Gamer & Büchel, 2012; Ditzen, Schaer, Gabriel, Bodenmann, Ehlert, & Heinrichs, 2008), while psychopaths themselves show dampened amygdalar activity (Gao et al., 2009) and structure (Weber et al., 2008). Though paradoxical at this point in time, further investigation into the link will certainly be necessary to clarify pertinent questions.

What are unclear are certain aspects of oxytocin's effect on the body as a whole. Inverse relationship between oxytocin and testosterone have been formally discussed (see Fisher, 1998) as well as informally--that is, behavioral effects of OT and testosterone

have been tested independently and inverse behaviors have been clearly demonstrated (see Bos, Terberg, & van Honk, 2010 vs. Kosfeld et al. 2005). Oxytocin antagonists increase aggressive behavior in dam rats (Lubin, Elliot, Black, & Johns, 2003) as does exogenous testosterone administration (Hermans, Ramsey, & van Honk, 2008). Indeed, subjects with higher testosterone commit more violent crimes (Dabbs, Jurkovic, & Frady, 1991), are generally more aggressive (McDermott, Johnson, Cowden, & Rosen, 2007) and decrease cognitive empathy in women (van Honk, Schutter, Bos, Kruijt, Lentjes, & Baron-Cohen, 2011). Even more curious is the link between OT, testosterone, and anxiety. Holi et al. (2006) found reduced cortisol levels in young adult male psychopathic offenders with an established history of violence; similarly, Cima, Smeets, & Jelicic (2008) showed lower mean levels of cortisol (daily) in a group of psychopathic offenders. This is curiously similar to the effects of oxytocin's anxiolytic effects (Grewen & Light, 2011; Domes, Heinrichs, Glascher, Buchel, Braus, Herpertz, 2007; Ditzen, Schaer, Gabriel, Bodenmann, Ehlert, & Heinrichs, 2009). Though it is clear that there is a link between oxytocin and testosterone, it is also clear that the connection is not direct nor is the relationship between the two linear. More research involving the biochemical connection between the two needs to be done before any conclusion is drawn regarding the link between psychopathy and OT.

Taken together, OT has shown itself very relevant in prominent clinical disorders and the OT's potential as a therapeutic drug for many of the aforementioned disorders is worthy of more attention. However, as mentioned, its discussion in the context of psychopathy is lacking. Lubin, et al. (2003) that found that dam rats infused with 1,000ng of an oxytocin antagonist increased maternal aggressive behavior towards intruder males,

including a faster onset of aggression, yet did not show any statistically significant changes in maternal or other behaviors. Shamay-Tsoory et al. (2009) also demonstrated that increased OT by intranasal spray did increase certain antisocial behaviors. Though schadenfreude as a construct has not been prominently discussed in the context of psychopathy, it certainly relates to the lack of empathy for others shown in psychopathic individuals. Taken together, it is clear that it is logical assume that a mental disorder characterized in part by decreased empathy, inability to infer emotional states, decreased eye gaze, and low attachment (Hare, 2003; Dadds et al., 2008) would have some dysregluation with OT, a neuropeptide that promotes these qualities (Bartz, Zaki, Bolger, Hollander, Ludwig, Kolevzon, & Ochsner, 2010; Guastella, Mitchell, & Dadds, 2008). Though the role OT plays in mental illness remains unclear and our understanding is in its infancy, by looking at the relationship between OT and psychopathy, our understanding of both OT and the neurobiological substrates of psychopathy will certainly broaden. Potentially, it may also provide one of the first few steps in pharmacotherapeutic research for psychopathy as well as serve as a biomarker for such emotional disorders.

Yawning and Psychopathy

Yawning is a stereotyped behavior that, in our evolutionary history, has clear, deep roots as evidenced by its proliferation in mammals as well as many other vertebrates (Argiolas & Melis, 1998; Lehmann, 1979). It is clearly characterized by long inspiration followed by a shorter expiration (Argiolas & Melis, 1998). While literature concerning the pharmacology and functional anatomy of yawning is not lacking (Nahab, Hattori, Saad, & Hallett, 2009; Argiolas & Melis, 1998; Guggisberg, Mathis, Schnider, & Hess,

2010), the primary facet of yawning of interest is the phenomena of contagious yawns, specifically within the context of psychopathology.

Contagious yawns, which are spurred by yawn, thinking, hearing, reading, or seeing observing another conspecific (or other species), have been strongly linked to empathy (Platek, Mohamed, & Gallup, 2005; Platek, Critton, Myers, & Gallup, 2003; Lehnmann, 1979). They are even well documented in other higher primates such as *Pan Troglodytes* and, too, are liked to empathy (Campell & Waal, 2011). Interestingly, Schürmann and colleagues (2005) found that the mirror-neuron system is not directly activated in contagious yawning, suggesting that the action is automatic and not imitated. Norscia and Palagi (2011) found that people show a large susceptibility to contagious yawns when elicited by a related individual in terms of occurrence and frequency of yawns. For strangers, they found that people show a marked latency period of contagious yawns, strongly suggesting a component of familiarity involved with the contagion.

Conclusions

Given the empathetically facilitative properties of the endogenous peptide oxytocin as well as the marked behavior changes that occur by intranasal administration of OT, we hypothesize that intranasal oxytocin administration (48IU) will increase the startle potentiation in subjects high on psychopathic traits, a population with particular antisocial characteristics that include a flattened affect and low empathetic capacity (Hare, 2003), in a startle paradigm nearly identical by Anderson, Stanford, Wan, and Young (2011). Affective potentiation of the acoustic startle reflex is one the most prominent psychophysiological measures of amygdalar responsiveness (Lang, Bradley, & Cuthbert, 1990; Davis, 1989; LeDoux, Iwata, Cicchetti, & Reis, 1988). Psychopaths

reliably demonstrate an impairment of potentiation of the startle reflex (Patrick, Bradley, & Lang, 1993), while healthy controls reliably potentiate with negative affective valence and attenuate the fear response with positive affective valences (Lang, Bradley, & Cuthbert, 1990). What's more, Patrick and colleagues (1993, 1994) connected the lack of potentiated startle in psychopathy to the emotional facet of the PCL-R (Hare, 2003) while the antisocial facet was found to be unrelated. To our knowledge, such an examination has not been done in high psychopathic trait individuals. In our case, we will compare individuals that are low on psychopathic traits to those high on psychopathic traits in a single-blind, placebo-controlled model.

Finally, individuals with Autism Spectrum Disorder, who have been found to have empathic deficits (Baron-Cohen, Kickermeyer, & Belmonte, 2005), show a dampened susceptibility to contagious yawning (Helt, Eigsti, Snyder, & Fein, 2010; Senju, Maeda, Kikuchi, Hasegawa, Tojo, & Osanai, 2007). While a direct connection between ASD and psychopathy is not being made, it is of interest that there is symptomatic overlap between the two conditions. Given, however, that there has been shown that decreased susceptibility to contagious yawning is seen in ASD, we wish to investigate the connection between psychopathy and contagious yawning; that is, we hypothesize that individuals scoring high on the PPI-R will be less susceptible to contagious yawns when compared to low psychopathic individuals as a function of empathic sensitivity.

As mentioned, such an investigation involving administering intranasal OT to individuals high on psychopathic traits has, to our knowledge, not yet been examined. Our results will be of interest regardless of what is found. Further, it will serve as strong

preliminary data for future research involving psychopathy and OT. In the literature, there is much speculation that oxytocin dysregulation is involved in mental disorders (Bora et al., 2009) and it is logical to suspect that intranasal administration may improve the deficits psychopaths demonstrate in a startle task.

CHAPTER TWO

Methods

In these experiments, a total of 133 college male and female participants were selected based on their scores on the PPI-R. A high psychopathy (HP) group was established by taking participants who score above the mean in a male college sample (Lilienfeld & Widows, 2005). Conversely, those who score low on the PPI-R will be grouped into a low trait group (LP). These experiments consisted of two separate paradigms: a yawning task and an emotion-related startle paradigm.

Experiment One: Yawn

Participants

For the yawning paradigm, one hundred and thirty five university males (n = 57) and females (n = 78) were used. In this particular experiment, the HP group was established as a score greater than or equal to the 65th percentile, which is the cut-off range for clinical diagnoses of psychopathy (Lilienfeld & Widows, 2005). For this experiment, groups were selected on their overall score on the PPI-R. The two groups experienced the same treatment intended to induce yawns.

Yawn Paradigm

Videos of individual males and females unknown to any participants were selected to provide 7-10 second videos of a yawn, a laugh, or a neutral face. This paradigm follows the methods listed in Platek, Mohamed, Gallup (2005), a method

shown to induce yawns. Participants viewed a series of video blocks consisting of three videos containing a random ordering of yawning, laughing, or neutral clips. To be clear, each video block did not contain the videos from one individual, but rather a pseudo-random and exhaustive selection of yawns, laughs, or neutrals from the pool of videos recorded from the strangers. Each individual video was 7-10 seconds long and each block was 24-33 seconds long (with a one second interval between each video in the video block). Ten seconds of a blank black screen separated each block and participants viewed 20 blocks.

Procedure

Participants were instructed to sit in a padded chair in a dimly lit, radiofrequency anechoic chamber (Raymond EMC Enclosures Ltd. Ottawa). Participants were sat in front of a computer monitor and instructed to wear noise cancelling headphones. They were asked to relax for one minute's time. They were told that they would be watching a movie of different people's expressions, that they need to remain comfortably seated, and to keep their attention on the screen. Further, if they felt the need to adjust themselves, laugh, cough, yawn, or blink, that they were allowed to do so as long as their attention remained on the screen and that they would return to a still, comfortable position.

Unlike Platek et al. (2005), we were simply interested in inducing yawns. As a validation measure, a facial electromyogram (EMG) and direct video observation of the participant were utilized. Duration of yawns was also measured. EMG took recordings from the orbicularis oculi muscle of the participant's right eye. A pair of Ag-AgCl electrodes (Biopac Systems Inc., Goleta, CA, USA) was placed one centimeter below the eyelid, with one directly below the pupil and the other one centimeter to the right of the

first. A third electrode was placed directly in the middle of the forehead to serve as a ground. Prior to placing the electrodes, skin was prepared with an isopropyl alcohol rub and a mildly abrasive gel (NuPrep) to improve surface conductance. Signa gel brand saline gel was used as a conducting medium and impedances were kept below 5 kΩ. Hardware used to collect EMG signals was BioPac MP150 data acquisition hardware using a sampling rate of 2000Hz and a 10-500Hz bandpass filter. EMG data was rectified and integrated with a time constant of 10ms. Data will be recorded with AcqKnowledge 3.9 software (BioPac Systems Inc.).

After the task, a short questionnaire was given to participants in order to determine if they actively prevented a contagious yawn during the paradigm. At this time, the participants were allowed to stand-up and stretch if they choose to do so.

Experiment Two: Startle

Participants

For the startle-paradigm, a single-blind, drug-placebo format between both LP and HP in a male university sample was used. An all-male sample of was used and collected by an online screening program. Participants were male so as to avoid possible confounding hormonal changes that would have to be controlled for in female participants as well as the issue of possible pregnancy related issues involving oxytocin administration.

Startle

A startle paradigm established by Anderson et al. (2011) was used to measure emotion-modulated startle. Affective pictures from the International Affective Picture

System (IAPS; Lang, Ohman, & Vaitl, 1988) were utilized. The images have standardized ratings of affective valence and arousal level (Lang & Greenwald, 1988). An equal number of IAPS pictures for positive, negative, and neutral will be used (45 total). The particular set of images used in the current paradigm were selected from a pool previously used in a study by Larson, Ruffalo, Nietert, and Davidson (2005), which had verified test-retest reliability in measuring emotion-modulated startle. Anderson et al. (2011) describes picture selection and exclusion criteria for the IAPS images to be used in the paradigm.

Participants were instructed to administer 48 IU of fluid, synthetic oxytocin or saline (0.8ml), via nasal atomizer (MAD 300, LMA), one in each nostril, and asked to keep the spray in their sinuses by "sniffing". No less than 10 minutes passed between solution administration and the beginning of the paradigm so as to allow the substance to reach the target site. Participants were instructed to sit in a padded chair in a dimly lit, radiofrequency anechoic chamber (Raymond EMC Enclosures Ltd. Ottawa), which is designed to minimize unnecessary electromagnetic waves that would potentially interfere with equipment recordings. Participants put on noise-cancelling headphones, through which the startle burst was delivered. They were sat in front of a computer monitor and were instructed to relax for one minute. Participants then were instructed to keep their full attention on the screen during the entire presentation and were informed that they were going to hear a burst of white-noise through their earphones, which is to be ignored. Pictures were presented pseudo-randomly in a single block of 60 images. The order of the pictures was such that no two pictures were presented serially.

Pictures were on screen for 6 seconds and followed by a 2 second interstimulus interval which will consist of a white plus sign (+) in the middle of a black screen for the participant to focus. Thirty of the pictures contained a white noise burst, which lasted 50ms at 100dB. Startle probes were assigned randomly to images with an equal number of probes assigned to each valence category. There were fifteen images per valence category with ten paired with the startle probe, which was delivered either 3s or 5s after the onset of the image. Software used to present the startle paradigm was Superlab 4.0 (Cedrus Corporation, San Pedro, CA, USA).

EMG was used to measure the magnitude of the startle response with the same preparation as mentioned in the yawning paradigm. Blink magnitudes were defined as smoothed EMG signal, recorded as baseline to peak differences for each startle probe. In order to establish a baseline, the mean orbicularis oculi EMG reading during the 25ms prior onset of the noise was used; amplitude peaks of interest were defined as the maximum amplitude between 40ms and 120ms after the onset of the noise.

Statistics and Analysis

This investigation used a 2 (drug vs. placebo) X 2 (low traits vs. high traits) generalized randomized block design, where psychopathy is expected to moderate the effect of drug during the startle task. We also followed up with tests of simple main effects of drug and psychopathic traits, where an interaction is predicted. For the yawing paradigm, chi-squared tests were performed between high and low traits of certain sub-factors of the PPI-R and susceptibility to a contagious yawn.

It is important to note that prior to analysis, raw peaks were standardized within subjects due to the high variability of blink amplitude variation. Further, parametric tests

were done with difference scores (DS), defined as the mean peak amplitude for neutral stimuli less the mean peak amplitude for negative stimuli (see Anderson et. al., 2011). Lower numerical values of DS would suggest more potentiated reactions to negative stimuli. Higher numerical values would suggest less potentiation to negative stimuli, as the mean peak amplitude for negative stimuli would be a smaller value.

A calculation of effect size derived from the main effects of drug of similar studies involving the use of intranasal OT yielded a mean, medium effect size of f = 0.2802 (Guastella et al, 2008, 2009; Kirsch et al., 2005; Jesso et al, 2011; Shamay-Tsoory et al., 2009; Fisher-Shofty et al., 2010; De Dreu, 2012; Ellenbogen et al., 2012; Averbeck et al., 2012; Petrovic et al., 2008; Gamer & Büchel, 2012). Given this medium effect size, to maintain statistical power = 0.80, a minimum total sample size of n = 102 would be necessary.

CHAPTER THREE

Results

Experiment One

The mean age for the participants in this study was 18.89, SD =1.13. In terms of observed yawns (133) within the paradigm, the modal number of yawns was zero followed by 1, 2, and 3 yawns respectively (see Figure 1). Individuals with highly atypical Inconsistent Responding scores were removed from the analyses. As well, the invalid participants (listed in experiment 2) were also excluded. Females were more likely than males to yawn during the paradigm, but a statistically significant gender effect was not shown, $\chi^2(1, N = 123) = 1.335$, $p = .248$. Next, a test looking at susceptibility to yawn by high and low traits on the overall score of the PPI-R showed $\chi^2(1, N = 123) = 2.938$, $p = .087$, with individuals low on psychopathic traits yawning with greater relative frequency. Sub-factor tests showed $\chi^2(1, N = 123) = 1.423$, $p = .223$ for Fearless Dominance; Self-Centered Impulsivity showed $\chi^2(1, N = 123) = .244$, $p = .621$; and $\chi^2(1, N = 123) = 7.051$, $p = .008$ for Coldheartedness. Percentages and values are shown in Table 1.

The average number of yawns for a low-trait individual on the CD scale was $M = 3.36$, $SD = 3.72$, while the average number of yawns for individuals high on CD traits was $M = 1.96$, $SD = 3.11$. An independent samples t-test was performed between high and low trait participants on the Coldheartedness sub-factor and number of yawns showing, $t(121) = 2.184$, $p = .031$; CI(95%) = $.132 < \overline{x} < 2.680$, $d = 0.40$. Finally, when

the DS between the mean peak of neutral pictures and negative pictures was examined using a regression analysis (see experiment 2), the values were notably predictive of yawning frequency (β = -.383, p =.007).

Experiment Two

A total of 57 university males (mean age = 19.158, SD = 1.236) were used in this experiment. A total of 9 subjects were excluded from the analyses for various reasons including inability to administer the solution properly (n=1), lack of a startle reflex (n=1), and incomplete or invalid PPI-R scores (n=7). A test for the main effect of high and low trait groups did not show significance [$F(1, 47) = .366$, $p = .548$]; the same was seen with the main effect of OT [$F(1, 47) = .580$, $p = .450$]. Lastly, an interaction showed $F(1, 47) = .035$, $p = .853$.

CHAPTER FOUR

Discussion

Experiment One

While psychopathy is not simply the inversion of empathy, endorsement of the CD subscale is strongly indicative of damped empathic affect. The theory that contagious yawning in our species is largely mediated by empathy is supported by the significant difference between genders on probability of yawning (63.5% of women yawned compared to 53.1% of males), as females tend to consistently score higher on measures of empathy than males (Rueckert, Branch, & Doan, 2011). Further, as previously discussed, psychopathy is almost exclusively diagnosed in males. Therefore, it is expected that a higher percentage of females would yawn during the paradigm; however, since there was no statistical difference between genders, a gender effect on likelihood to yawn can be easily controlled. This difference merely shows that the paradigm itself maintains a level of validity consistent with the existing literature that would be expected.

When evaluating the subscales, only Coldheartedness yielded significance. This is not surprising considering that the grouping variables SCI or FD do not wholly encapsulate the emotional components (or lack thereof) of psychopathy and tend to focus on behavioral and interpersonal factors. A difference between groups suggests that increased CD is associated with decreased susceptibility to a contagious yawn. Further, when considering the overall PPI-R score, which includes all subscales,[1] a strong trend

[1] Machiavellian Egocentricism, Rebellious Nonconformity, Blame Externalization, Carefree Nonplanfulness, Social Influence, Fearlessness, Stress Immunity, & Coldheartedness

towards significance is seen, which is likely mediated by the CD subscale. When compared to other sub-factors, FD and SCI, Coldheartedness clearly maintains the largest affective component of the PPI-R (Lilienfeld & Widows, 2005). Lastly, significance of yawns between high and low Coldheartedness scores adds further support to the current data available on empathy and contagious yawning.

In line with theory and previously shown between genders, increased empathy is associated with increased susceptibility to contagious yawning (Platek, et. al., 2003). Using psychopathy as a predictor of susceptibility of contagious yawning may, then, be a viable avenue of research simply by virtue of the interpersonal and emotional abnormalities associated with psychopathy. The results of this experiment lend support to the theory that empathy and contagious yawning are highly intertwined in our species and work together to accomplish certain evolutionary goals.

Though only males were exposed to the startle paradigm, yawning data were collected on all participants. A regression analysis showed that the difference between the negative and neutral mean potentiation was predictive of yawning frequency (β = -.383, p =.007). Experiment 2 provides interesting physiological data and predictive parametric value to a future study. In this case, the lower the yawning susceptibility, the lower the difference between neutral potentiation and negative potentiation (resulting in an overall higher numerical value) will be. The negative correlation between the neutral-negative difference and yawning frequency shows that the higher the frequency of yawns, the greater the difference between the neutral-negative difference (resulting in a more negative numerical value). Thus, the greater the measured psychopathic traits, the lower the startle potentiation and, thus, the lower difference value between neutral and negative.

On the other hand, the less measured psychopathic traits, the greater the startle potentiation, which produces a greater difference value.

The relationship between startle potentiation and emotional dysregulation is well studied. Aside from the psychopathy-related research currently presented, startle potentiation is seen in emotional disorders involving increased (and dysregulated) emotional disposition including anxiety and depression (see Ballard, et al., 2014). Further, the empathy and stress reactivity have been shown to be modulated by oxytocin receptor gene variation (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Oxytocin is heavily implicated in modulating yawning behaviors in mammals when injected into the VTA (Sanna, Argiolas, & Melis, 2012). The available research gives sufficient pretense to the data collected in these experiments. Our data suggests that one's level of psychopathic traits and startle reactivity are related to one's susceptibility to contagious yawning. Both independent variables have a strong relationship in empathic behavior and emotional regulation.

Experiment Two

A preliminary look at the differences between the high and low trait groups showed no difference when groups were determined with a median split; thusly, there is a dim prospect for the addition of a drug-placebo component for the study. In the interest of time, sufficient group size to achieve adequate statistical power was not met. Further, Anderson et al. (2011) determined high and low groups based on the subscales Fearless Dominance and were able to show significant differences between startle potentiation. Our protocol called for a median split on the total PPI-R score. Increased participant

number should be sufficient to replicate the results seen in Anderson et al. Further, no main effect for intranasal oxytocin was seen.

Aside from lack of sufficient power, the route of administration of OT in this is experiment is called into question. It is difficult to determine with an acceptable degree of certainty if the OT is reaching its target site with consistency. The most notable drawback was the administration error generated by the participants, despite repeated demonstrations on how to administer the solution with the device. Other experiments involving intranasal OT administration report using a pump intranasal atomizer for delivery or often times a device unspecified. In our case, we used a standardized method of delivery, the MAD-300 nasal atomizer, which delivers a consistent, standardized dose of solution intranasally. Its use controls for inconsistencies in dose-per-pump of a conventional atomizer. However, the MAD-300 does not control for user-device variability nor the ability of the participant to properly hold the solution within the nasal sinuses for maximal absorption. These inconsistencies call into question the validity of insufflation as a delivery method. Sublingual absorption may be a more reliable method of OT administration into the bloodstream in a research setting.

Conclusion

To our knowledge, no experiments showing the relationship between startle potentiation, psychopathy, and yawning have been published. It is, however, well established the relationship between psychopathy and startle as well as the relationship between yawning and empathy (Norscia & Palagi, 2011). Though pilot in nature, our data suggests that the startle potentiation may predict one's susceptibility to contagious yawning. In line with the theories presented on yawning and startle, it is reasonable to

expect that low startle potentiation is related to yawning susceptibility, as affect is highly considered in both realms of research.

The results of these two experiments are clear indicators that psychopathy is a robust, multifaceted disposition, where a strict interpretation of an overall PPI-R score is not necessarily a predictive one. Rather, attention to subscales and, of course, clinical evaluations are clearly more appropriate for predictability. While gender effects between yawning susceptibility certainly exist, the gender effect is controlled in the current study. The emotional component of the PPI-R is likely the most relevant to the experiments carried out. While the overall measure is possibly too robust a measure for these purposes, it nonetheless lends support to the developing idea that psychopathy, empathy, and contagious yawning are related.

In the future, of course, greater power is necessary for results more representative of the actual case. Further, the use of females in the startle-yawn paradigm would be important to show the observations across genders. In terms of the drug administration, a more direct and consistent route should also be considered. Sublingual absorption is an attainable alternative, which should ensure a more reliable route of administration, as less solution is lost by ingestion. Clearly, these data are not grounds to leave the question of OT and psychopathic traits to rest, but rather provide insight into improvements to the experimental design.

APPENDIX

Table A.1. Chi-Square analysis.

Chi-Squared Analysis

	Percentage Yawned				
Scale	High traits	Low traits	χ^2	*df*	*p*
Total PPI-R	50.90%	66.20%	2.938	1	0.087
FD	56.10%	62.10%	0.453	1	0.501
SCI	61.50%	58.30%	0.113	1	0.736
CD	46%	68.40%	6.223	1	0.013

Note. Fearless Dominance (FD); Self-Centered Impulsivity (SCI); Coldheartedness (CD)

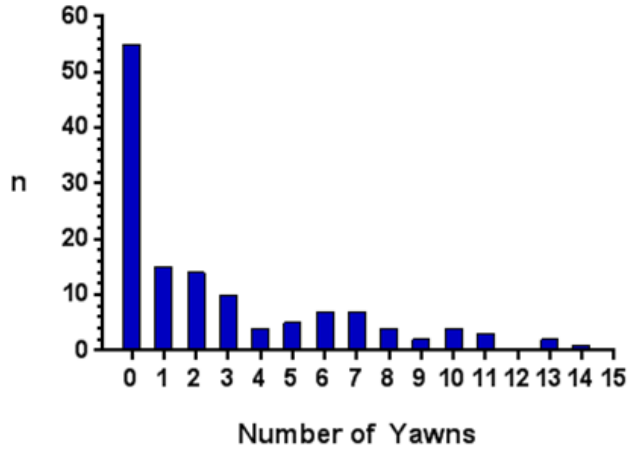

Figure A.1. Observed Yawning Frequencies.

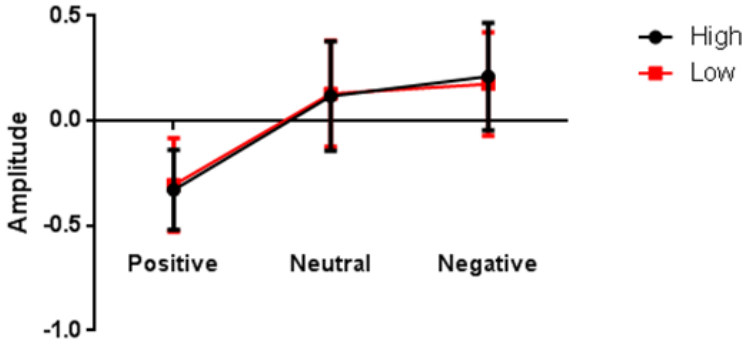

Figure A.2. Mean amplitudes for valence by high or low trait individuals

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