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Vijaya Reddy March 31, 2023

Long-term Impacts of Early Life Stress on the Functional Connectivity of Adult Emotional Neurocircuits in Rhesus Macaques

By

Vijaya L. Reddy

Mar M. Sanchez, Ph.D.
Advisor

Neuroscience and Behavioral Biology

Mar M. Sanchez, Ph.D.
Advisor

Kim Wallen, Ph.D.
Committee Member

Kristen E. Frenzel, Ph.D.
Committee Member

Megan F. Cole
Committee Member

Zsofia Kovacs-Balint, Ph.D.
Committee Member

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Abstract

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By: Vijaya L. Reddy

Child Maltreatment (MALT) is a traumatic form of early life adversity (ELA) with high prevalence in the United States and the grave physical threat it poses for infants and children. MALT is a major public health issue because it is associated with the development of physical illnesses, such as chronic inflammation and obesity, and mental illness later in life, including but limited to depression, anxiety, posttraumatic stress disorder -PTSD-, substance use disorder, and conduct disorder. This study examined the long-term effects of infant maltreatment (MALT) on adult functional connectivity (FC) between the amygdala (AMY), hippocampus (HIPP), and subregions of the prefrontal cortex (PFC) -mPFC, OFC, dlPFC, and vlPFC- due to the critical role of these circuits in emotional and stress regulation. For this, brain resting state functional MRI (rs-fMRI) scans were collected to examine ROI-ROI FC (AMY-AMY, AMY-PFC, AMY-HIPP, and HIPP-PFC). Our lab has previously reported greater anxiety in adult MALT animals using a measure of baseline amplitude of the acoustic startle reflex (Beesley et al, 2022), and the goal of this thesis was to identify alterations in PFC-AMY-HIPP FC that could underlie those effects. In addition, total COC intake during adolescence was added as a covariate to the statistical models to control for its potential developmental impact on FC in these cortico-limbic circuits during adolescence. The findings suggest that infant MALT did not have a long-term effect on adult AMY FC (AMY-AMY, AMY-PFC, or AMY-HIPP). The results also contrast with a previous publication from this cohort of animals studied from infancy to the juvenile, prepubertal, period (at 3, 6, 12 and 18 months of age), where weaker AMY-PFC FC was found in MALT than Control animals across development, particularly between AMY and subgenual cingulate (Area 25) anterior cingulate (Area 24), Area 13 in the

OFC and Area 9 in the dlPFC, whereas left AMY-right AMY FC was stronger in MALT than Controls (Morin et al, 2020). The findings in this thesis suggest transient effects of MALT on AMY FC during infancy and the juvenile period, with recovery ("catch up") of AMY-AMY and AMY-PFC typical FC underlying emotional regulation by adulthood. On the other hand, this study revealed long-term effects of MALT in HIPP-PFC FC, specifically between HIPP-Area 9 (dlPFC) and HIPP-Area 45 (vlPFC), and in both cases different in males than females; specifically, MALT females showed weaker negative FC than Control females, whereas the opposite directionality was observed in males. Adult anxiety was not associated with FC between HIPP and these two lateral PFC regions, suggesting functional alterations in other emotional regulation circuits that could underlie the exaggerated startle amplitude in the animals with ELS. Additional effects of Sex and Laterality were detected in the FC of AMY, PFC and HIPP circuits. Surprisingly, we did find a significant positive correlation between adolescence COC intake and AMY FC with vlPFC Area 47 FC , which is interesting given the vlPFC role in reward and reappraisal of addictive stimuli. Overall, these findings suggest long-term effects of infant MALT on specific HIPP-PFC circuit FC, but not AMY FC of adult rhesus monkeys, which contrasts with the weaker AMY-PFC FC reported in MALT animals compared to Controls during infancy and the juvenile period; this indicates that some effects of infant MALT on these corticolimbic functional development are temporary/transient, while others are long-term.

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Shreya Reddy

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INTRODUCTION:

The Effects of Child Maltreatment on Health Outcomes

Child Maltreatment (MALT) is a devastating form of early life adversity/stress (ELA/ELS), which involves abuse and neglect of a child under the age of 18 usually by an adult caregiver (World Health Organization 2022). In a national child MALT screening by the Children's Bureau of the U.S. Department of Health & Human Services in 2021, 588,329 out of ~3.0 million children were victims of MALT, with 76.0% of them experiencing neglect, 16.0% physical abuse and 10.1% sexual abuse (U.S. Department of Health & Human Services 2023). Despite many international studies and surveys, MALT remains difficult to study due to the various definitions/criteria used worldwide and across states in the US, as well as the challenges with reporting, substantiation and measuring instances of MALT; therefore, the current records of childhood MALT are most likely an underestimate. In addition to its high prevalence in the US (1 in 5 children in the US -DHHS, 2023) and the serious physical threat it poses for infants and children, MALT is a major public health issue because it is associated with the development of physical and mental illness later in life, including depression, anxiety, posttraumatic stress disorder -PTSD-, substance use disorder, ADHD, conduct disorder, criminal behavior and incarceration, as well as obesity and chronic inflammation (Tottenham et al.,2010; Winiarski et al.,2018; Moustafa et al., 2021; Danese & Tan 2014; Pace et al.,2006; Batten et al., 2004; Hayashi et al., 2015; Danese et al, 2007; Baldwin et al., 2023; Lo & Cheng 2015). Given the major burden of child MALT to individuals and society, it is important to analyze risk factors including socio-economic factors such as poverty, lack of employment and/or education-, lack of support network and genetic variables as well as protective/resilience factors for the occurrence of MALT and its outcomes (Sidebotham et al., 2006; Garbino & Kostelny 1992; Slack et al., 2017; Euser et al., 2010; Sserwanja et al., 2020; Spearman et al., 2022).

Does Child Maltreatment Alter Neurocircuitry Implicated in Emotional Regulation?

Despite the main link between child MALT and psychopathology later in life, the neurobiological

and developmental mechanisms that translate this adverse experience into mental and behavioral disorders are poorly understood. The specific focus of this thesis is on understanding how infant MALT results in long-term alterations in emotional and stress regulation in adulthood, leading to anxiety disorders. A main potential mechanism examined is that infant MALT alters the functional development of neural circuits underlying emotional and stress regulation, including key brain regions such as the amygdala (AMY), hippocampus (HIPP), and the prefrontal cortex (PFC). There is evidence that chronic, unrelenting and/or severe stress happening early in life -such as MALT- can, indeed, affect brain structural and, therefore, functional development of these PFC-AMY-HIPP neurocircuits critical for stress and emotional regulation, with long-term risk for mental illness (Howell & Sanchez, 2011; Wakeford et al, 2018; Teicher et al, 2003; Tottenham & Sheridan, 2009; Lupien et al, 2009).

Located in the temporal lobe just anterior to the HIPP, the AMY is a critical brain region for threat detection and the activation of appropriate stress and fear/anxiety-related behaviors in response to dangerous stimuli (Baxter & Croxson et al., 2012; Calder et al., 2001; Bliss-Moreau et al., 2011; Dal Monte et al., 2015). The primate AMY undergoes protracted structural and functional maturation extending from birth to early adolescence (Tottenham & Sheridan 2010; Chareyron et al., 2012; Lupien et al, 2009; Machado and Bachevalier, 2003; Payne et al, 2010;), which makes it susceptible to early adverse experiences that contribute to disrupted or altered AMY development (Schumann et al., 2019; Machado & Bachevalier et al., 2003; Gee et al., 2013; Avino et al., 2018; Totenham and Sheridan, 2010). Studies in individuals with bilateral amygdala lesions in a facial expression detection task show severe impairments recognizing fear in facial expressions (Adolphs et al., 1999; Adolphs et al., 1994; Calder 2010; Cardinale et al., 2021; Sprengelmeyer et al., 1999), stressing the critical role of the AMY in fear recognition. Amygdala Lesion studies in nonhuman primates (NHPs) show impaired threat detection as well as reduced learning and maintenance of fear associations (Dal Monte et al., 2015; Bauman et al., 2004; Amaral et al., 2002; Amaral et al., 2003; Medina et al., 2020). Additionally, neonatal AMY damage

delayed fear acquisition as measured by the fear-potentiated startle response (Kazama et al., 2013), which is a reflex that causes contraction of skeletal muscles for defensive, behavioral responses to an unexpected, fear-inducing stimulus (e.g. a loud noise); conversely, electrical stimulation of the AMY leads to an elevated amplitude of the acoustic startle reflex (Angrilli et al., 1996; Davis et al., 1997; Hitchcock, J.M. & Davis, M. 1991; Rosen J.B. & Davis, M. 1988). The acoustic startle amplitude is an established and translational biomarker for anxiety and emotional reactivity in human and animal models (Shalev et al, 2000; Sanchez et al, 2005), with higher startle amplitude reported in populations with anxiety disorders (Coleman & Pierre, 2014) and in NHP models of ELS including the infant MALT model studied in this thesis (Beesley et al, 2022; Sanchez et al, 2005). Despite its strong role in threat detection and fear acquisition and expression, the AMY structural and functional alterations reported in MALT human and NHP populations are inconsistent -i.e. studies report increased, decreased or no change in amygdala volumes- (Hanson et al., 2015; Howell et al., 2014; McEwen, 2005; Teicher et al., 2016; Tottenham and Sheridan, 2010); however, many of those studies focused on children and adolescents. Some authors have proposed the possibility that ELA-related alterations on amygdala volume may only be detected after adolescence (Nelson, 2013; Tottenham & Sheridan, 2010). Supporting the latter possibility, Dutcher and collaborators (2023) found larger AMY volumes in adult rats who experienced a different form of ELA (repeated maternal separation), which may underlie the increased sensitivity to stressors in the animals with ELA.

Located in the medial temporal lobe, the hippocampus (HIPP) has critical roles in learning and declarative memory and spatial navigation (Squire et al., 1992), but it is also involved in emotional processing and memory regulation (Zhu et al., 2019; Anangnostaras et al., 2001). Hippocampal lesions in rhesus monkeys reduced fear expression in monkeys, demonstrating that hippocampus may be critical for learning and maintenance of fear (Chudasama et al., 2008). Although the primate HIPP, similar to the AMY, shows a protracted structural and functional development up until adolescence

(Gomez & Edgin 2016; Payne et al, 2010), elements of hippocampal function have been noted in infant behavioral patterns, such as object recognition memory (Robinson & Pascalis 2004). In addition, the HIPP is critical for inhibition of the hypothalamic-pituitary-adrenal (HPA) axis -the major neuroendocrine stress system (Jacobson & Sapolsky 1991)- through negative feedback mediated by its high levels of glucocorticoid receptors-GRs- (Herman et al., 2016).. Due to its extended period of development and high expression of GRs, the HIPP is very vulnerable to ELS and other adverse environmental/social factors that may alter HIPP development, including decreased hippocampal volumes (Bremner et al., 1995; Hanson et al., 2015; Herman et al., 2005; Sanchez, 2006; Tottenham & Sheridan, 2010; Humphreys et al., 2018)). Consistent with that literature, children exposed to MALT also exhibit reduced hippocampal volumes as adults (Woon and Hedges et al., 2008; Gorka et al., 2014), which has been linked to increased emotional sensitivity to stress as well as deficits in memory performance (Frodl et al., 2006; Hickie et al., 2005).

Located in the most anterior section of the frontal lobe, the PFC is a multifaceted region, comprised of multiple subregions (medial PFC -mPFC-, orbitofrontal cortex -OFC-, dorsolateral PFC -dlPFC-, and ventrolateral PFC -vlPFC-) broadly implicated in behavioral organization, executive function, and emotional and stress regulation (Fuster 2001). Even though the PFC neurons are produced before birth, the structural maturation of the PFC, including neuronal differentiation, synaptogenesis, pruning and myelination extends into young adulthood in primates, including humans (Kolk & Rakic 2021; Lenroot and Giedd, 2006; Teffer & Semendeferi 2022). Due to this protracted structural and functional maturation, the PFC is highly susceptive to environmental and social chronic stressors that may alter its developmental trajectory, which is known to contribute to negative health outcomes later in life, such as greater adult anxiety and elevated emotional reactivity (Arnsten 2010; Woo et al., 2021; Cerqueira et al., 2007; Guadagno et al., 2021; Ohta et al., 2020). Several studies highlight how during its extended maturation process, PFC increasingly exerts critical top-down inhibitory control over amygdala activation

in response to threats and stressors, which is critical for emotional regulation (Motzkin et al., 2015; Ghashhaei & Barbas 2002; Hare et al., 2008; Levesque, et al., 2004). Thus, this raises the potential for ELS, such as child abuse and neglect, to affect PFC structural and functional development, which is supported by the literature reporting significant negative correlations between ELS stress and PFC volumes (Frodl et al., 2010) as well as associations between ELS and disrupted PFC regulation of the AMY (see AMY-PFC section for more details). Additionally, a rich literature supports the involvement of the mPFC, particularly its ventromedial PFC (vmPFC) component- as heavily involved in emotional responses through strong connections to the amygdala and hippocampus (Arnsten, 2009; Tottenham & Sheridan, 2010) and in retention of fear extinction (Morgan et al., 1993; Phelps et al., 2004; Sotres-Bayon et al., 2006; Rauch et al., 2006; Milad and Quirk et al., 2002). In addition to regulating fear extinction, the mPFC is also a major player in assigning affective/emotional meaning to integrated sensory and conceptual information (Roy et al., 2012; Gusnard et al., 2001; Lane et al., 1977). Ochsner et al., 2004 stresses how the enhancement of emotion is mediated by mPFC activation, while down-regulation of emotion is modulated by the OFC, which is known for its unique role in behavioral inhibition and decision-making (Rogers et al., 1999; Doherty et al., 2003). Along with the mPFC, the dlPFC is involved in control of attention, decision-making, assigning valence to emotional stimuli and top-down emotional regulation of the AMY, particularly inhibition of intense impulses of fear and aggression (Zwanzger et al., 2014; Notzon et al., 2017). Similar to the OFC, the vlPFC is associated with inhibition of non-desired behaviors (Aron et al., 2004), but it is also particularly recruited during reappraisal -the process by which people alter their interpretation of a known stimulus- (Wager et al., 2008; Hui et al., 2022). Individuals that experienced ELA, including child MALT, have smaller PFC volumes as well as impaired functionality (Arnsten, 2009; Funahashi & Andreau, 2013; Hanson et al., 2012). To potentiate the fear response, particularly in individuals who have experienced MALT, the AMY- HIPP-PFC work together to regulate the acquisition, consolidation, and extinction of contextual fear memories

(Chaaya et al., 2018; Fendt & Fanselow 1999; Takita & Izawa-Sugaya 2021; Rudy et al., 2004; Maren & Fanselow 1995; Maren et al 2013; Maier et al 2020; Shin & Liberzon 2009; Spalding 2018), suggesting the AMY, HIPP, PFC must be structurally connected and/or functionally correlated. Indeed, extensive literature supports structural and functional connectivity (FC) in the AMY-HIPP-PFC network. Anatomical studies reveal afferent polysynaptic axonal projections from the HIPP to the basolateral AMY (Maren & Fanselow 1995; Otterson 1982), and major efferent monosynaptic and polysynaptic axonal projections from the HIPP to the PFC are commonly reported as the HIPP-PFC circuit, which is known to play a significant role in emotional regulation (Li et al., 2015; Godsil et al., 2012; Rosene & Hoesen 1977; Ruggiero et al., 2021). Although there are multiple white matter tracts connecting the AMY and PFC, the uncinate fasciculus (UF) is a major monosynaptic, bidirectional, long-range white matter tract that specifically links the vmPFC and OFC to regions in the temporal lobe in NHPs and humans, (Von der Heide et al., 2013; Swartz et al .,2013; Olson et al., 2015; Schmahmann & Pandya, 2009; Schmahmann et al., 2007). There is controversy over whether the UF also connects the hippocampus to the frontal regions of the brain as anatomical literature does not support projection into the hippocampus (Von der Heide et al., 2013; Schmahmann and Pandya 2009). The UF tract is involved in emotional regulation (Von Der Heide, Skipper, McFarlin, & Olson, 2013) and anxious temperament (Baur, Hanggi, and Jancke 2012; Kim & Whalen 2009).

In addition to the structural links between the AMY, HIPP, and PFC, these regions also exhibit strong FC with each other, particularly in response to threatening or emotional stimuli (Gold et al., 2015; Morawetz et al., 2017; Morris et al., 1999). Briefly, FC refers to the correlation of the temporal changes in blood-oxygen-level-dependent (BOLD) signal across two brain regions, and the valence of the FC carries tremendous significance. While positive FC between two brain regions means that the regions are positively coupled (work in synchrony), negative FC is thought to reflect negative coupling between

two brain regions (i.e. activation in one brain region will happen with inhibition activity on the second region).

AMY-PFC FC

During typical child development, the human mPFC and AMY show positive FC (coupling), which is considered to be an immature connectivity (Gee et al., 2013); our group has replicated a similar developmental phenomenon in infant macaques (Morin et al, 2020). As humans transition from child to adolescence, there is a developmental shift to a "mature", inversely correlated (anticorrelated; negatively coupled) AMY-mPFC FC (Wu et al., 2016; Gee at al., 2013; Park et al., 2018). The "mature" negative AMY-mPFC is consistent with reports of downregulation of AMY activation by the mPFC via top-down inhibitory control in response to stressors or threats (Kim et al., 2011; Quirk et al., 2003; Rosenkranz and Grace 2002; Andrewes and Jenkins et al., 2019). Interestingly, as Gee at al., 2013 notes, individuals that experienced ELA exhibit a mature (i.e. inverse correlation -negative coupling-) AMY-mPFC FC earlier -during childhood-, suggesting that ELA may trigger an accelerated AMY-mPFC FC maturation, which may be a biomarker for psychopathologies later in life. An important question this thesis will address is whether negative FC will be also prevalent during adulthood. Apart from this interesting issue of developmental changes in FC valence (from positive FC in childhood to negative FC in adults), ELA is consistently associated with weakened AMY-mPFC FC in young and adult rodents, NHPs, and humans, which in turn is predictive of increased anxiety and poor emotional regulation (Guadagno et al., 2018; Park et al., 2018; Birn et al., 2014; Javanbakht et al., 2015; Fan et al., 2014; Morin et al, 2020). In contrast to the AMY-mPFC, there are very few studies that report the impact of ELA on AMY-dlPFC or AMY-vlPFC. Greater threat-related ELA based on peer aggression or parental abuse up until 13 years of age, has been associated with stronger negative AMY-dlPFC resting state FC during adulthood (Kaiser et al, 2017). ELA in the form of childhood poverty, on the other hand, has been associated reduced AMY-dlPFC and AMY-vlPFC coupling in adults, suggesting ELA triggers deficits in regulating

emotion (Kim et al, 2013). To our knowledge, there are no published studies in humans that examines the consequences of ELA on AMY-OFC FC, although it results in thinning of the OFC, which is partially mediated by symptoms of depression in adulthood (Monninger et al., 2020). Because there is evidence that the OFC is heavily involved in decoding reward and emotional states particularly in decision-making (Rolls et al., 2020), this thesis will examine whether infant MALT in macaques results in long-term alterations in adult AMY-OFC FC.

AMY-HIPP FC

In typically developing human infants, AMY-HIPP FC -as shown above for AMY-PFC FC-, is positive, peaking in adolescence and then becoming weaker with age (St. Jacques et al., 2009; Barch et al., 2017). This pattern supports the view that AMY-HIPP FC may play a crucial role in various types of memory, such as working memory, declarative memory, and memory of emotional stimuli, which also increase from infancy to adolescence and decrease with age (de Voogd et al., 2017; Stam et al., 2022; Fandakova et al., 2014; Pauls et al., 2013). The interactions between the AMY and HIPP -which closely regulate baseline/circadian HPA axis function-, are crucial to the strengthening of contextual fear memories (Herman et al, 2005; Kim & Cho 2020; Tottenham and Sheridan 2010). Although it is not clear how exactly the AMY-HIPP FC contributes to memory consolidation via regulation of the HPA axis, some studies indicate that stronger positive AMY-HIPP coupling is associated with abnormal HPA axis activity (Kiem et al., 2013; Vaisvaser et al., 2013), suggesting that AMY-HIPP coupling may play important role in modulating transient stress responses. Other studies report positive associations between strong positive AMY-HIPP FC and stress-induced memory enhancements (de Voogd et al., 2017; Dolcos et al., 2005), implying that robust positive AMY-HIPP connectivity may be an indicator of elevated fear and anxiety memories. Altogether, the evidence presented here supports the view that stronger positive AMY-HIPP FC may be a biomarker for heightened anxiety phenotypes. The limited literature on ELA effects on adult AMY-HIPP FC is consistent with that view, highlighting that individuals who have

experienced ELA in the form of child MALT, show increased AMY-HIPP FC during adulthood (Maier et al., 2015; Fan et al., 2015).

HIPP-PFC FC

The HIPP-PFC circuit plays a pivotal role in executive emotional modulation, and alterations in HIPP-PFC FC are associated with negative neuropsychiatric outcomes, such as schizophrenia, depression and other psychiatric disorders stemming from early life trauma or adversity (Ruggiero et al., 2021; Sigurdsson and Durvaci 2016). Patients with schizophrenia show weakened HIPP-mPFC and HIPP-dlPFC FC compared to healthy controls, suggesting HIPP-PFC may be a potential indicator for schizophrenic symptoms (Liu et al., 2019; Rasetti et al., 2011; Henseler et al., 2010). Individuals with major depressive disorder also exhibit impaired HIPP-dlPFC, HIPP-mPFC, HIPP-vlPFC and HIPP-OFC FC compared to controls, suggesting that a strong negative coupling between the HIPP-PFC is crucial for emotional regulation (Cao et al., 2012; Tahmasian et al., 2013; Kemmotsu et al., 2013; Zhou et al., 2022). Furthermore, child MALT is associated with reduced HIPP-mPFC FC during adolescence in both sexes, which predicts increased adolescent internalizing symptoms that are associated with a higher risk for depression and anxiety (Herringa et al, 2013). Weakened HIPP-dlPFC and HIPP-vlPFC FC are also reported in adults who suffered severe childhood stress, and the decreased FC between the HIPP and lateral PFC was found to be one of the factors that mediated the relationship between childhood adversity and deficits in autobiographical memory (Hakamata et al., 2021). Similar to the AMY-OFC, HIPP-OFC FC studies in MALT humans are limited, but there is evidence that children who experienced abusive parental care show smaller OFC volumes later in life (Hanson et al., 2010).

Translational NHP Model of Infant Maltreatment

As detailed above, there exists a robust association between ELA and alterations in FC in the AMY-HIPP-PFC neurocircuitry, which often predicts psychopathologies later in life, including but not limited to anxiety disorders, depression, substance abuse, schizophrenia. Studying the long-term neurobiological

effects of ELA in adulthood is challenging in humans due to issues with retrospective memories, lack of experimental control, the fact that many children exposed to child MALT experience repeated trauma through revictimization and may also be exposed to a multitude of stressors later in life, and the potential environmental confounding factors (e.g. prenatal drug/alcohol exposure, socioeconomic status – SES-, access to education and health care). As an alternative, this study focuses on a translational NHP model using rhesus monkeys (*Macaca mulatta*) to assess the questions raised in human studies through longitudinal, prospective experimental designs that employ random assignment of infants at birth to group and collection of behavioral measures from infancy through the juvenile period. Additional advantages of using rhesus monkeys for this study are their complex social behaviors, including mother-infant relationships as well as the feasibility to employ longitudinal magnetic resonance imaging (MRI) techniques to successfully examine the effects of infant MALT on brain development later in life (Howell & Sanchez, 2011; Sanchez, 2006; Sanchez et al., 2001). Furthermore, rhesus serve as great model organisms to conduct neurodevelopmental research because they share many phylogenetical, neural, physiological, and behavioral homologies with humans (Fedorenko and Blank, 2020), particularly the critical dependence of infants toward their mothers not only for nutrition and protection, but to develop critical attachment, social skills, behavioral control and emotional regulation (Maestripieri et al., 2009). Macaque mother-infant attachment, as in humans, is key to offspring neurobehavioral development (Hinde & Spencer-Booth, 1967). Adverse maternal care in the form of infant maltreatment, comprising of neglect and physical abuse, occurs naturally in NHP species with prevalence rates of 2-5% (Brent et al., 2002; Johnson et al., 1996; Maestripieri & Carroll, 1998; Sanchez, 2006; Troisi & D'Amato, 1984; Morin et al., 2020). The spontaneous rhesus model of infant MALT used in this study is operationalized as both physical abuse and comorbid rejection towards the infant by the mother during the first six months of life, which results in elevated infant anxiety and distress behaviors (Maestripieri & Carroll, 1998; Maestripieri, 1999; McCormack et al., 2009; McCormack et al., 2006; Sanchez, 2006; Morin et al.,

2020). As seen in humans, infant MALT seems to be a maternal trait that is repeated with subsequent offspring and shows transgenerational transmission through the maternal line (Maestripieri & Carroll, 1998; Maestripieri, 2005), which further supports this NHP model for use in translational neurodevelopmental studies (Franklin et al., 2010; Maestripieri, 2005; Tarullo & Gunnar, 2006). Macaque infant studies have reported negative health outcomes identified in human children who suffered child MALT, including increased anxiety, emotional reactivity, impaired impulse control, social deficits, elevated levels of stress hormones indicative of chronic stress exposure, activation of pro-inflammatory pathways, and larger amygdala volumes (Drury et al., 2017; Howell et al., 2019; Howell et al., 2014; Howell et al., 2013; Koch et al., 2014; Maestripieri, 1998; McCormack et al., 2009; McCormack et al., 2006; Morin et al., 2019; Petrullo et al., 2016b; Sanchez, 2006; Sanchez et al., 2010). Repeated exposure to elevated levels of cortisol, for example, could have multiple downstream neurodevelopmental alterations, including effects on the microstructural organization of white matter tracts of the AMY-HIPP-PFC circuits described above, leading to subsequent impacts in FC between these regions (Howell et al., 2013), providing one potential neurobiological mechanism as to how infant maltreatment can affect functional brain development and, therefore, anxiety behaviors later in life.

ELS increases risk for Substance Use Disorders during Adolescence

ELS serves as one of the major risk factors of adolescent initiation of drug use, constituting a "double hit" in terms of the consequences of MALT and drugs on key PFC-AMY-HIPP corticolimbic circuit development during adolescence on top of ongoing alterations in the neurodevelopmental processes from infancy through the juvenile period (Wakeford et al., 2018). While greater PFC functional impairment increases susceptibility to drug addiction, drug consumption also fuels further impairment of the PFC (Goldstein & Volkow 2011). Additionally, decreased PFC-AMY FC was found to predict depressant and psychostimulant drug use among adolescents (Crane et al., 2018; Crunelle et al., 2015). Therefore, adolescent drug intake, if compounded by the impacts of ELA, is a large threat to adolescents

and their vulnerability to comorbid mental disorders, such as anxiety and depression (Anthony & Petronis, 1995). This is why the Sanchez lab carried out a study to examine whether rhesus monkeys that experienced infant MALT showed greater susceptibility to cocaine self-administration (COC SA) during adolescence, compared to control macaques (Wakeford et al., 2019). Although no significant differences in total COC intake were found between the MALT and control macaques (unpublished data), this study incorporated total COC intake as a covariate in the statistical analysis, to control for potential effects of exposure to this psychostimulant during adolescence on the functional connectivity between the regions of interest.

Goals & Hypotheses

This thesis is a continuation of a longitudinal study of the effects of ELS on the structural and functional development of the AMY-PFC-HIPP neurocircuitry that underlies emotional regulation and increases risk for adolescent drug consumption. The **goal** of this study was to use a translational NHP model of infant MALT to examine the long-term effects of this ELS on adult PFC-AMY-HIPP FC which could underlie the elevated anxiety reported in the adult MALT animals (Beesley et al, 2022). Connectivity with the PFC was examined as FC with different functional subdivisions (mPFC, dlPFC, vlPFC, and OFC) based on their unique role in emotional regulation. We collected resting state functional MRI (rs-fMRI) data to examine FC using an ROI-ROI FC analysis. We also examined whether alterations in PFC-AMY-HIPP FC were associated with the elevated anxiety (exaggerated amplitude of the acoustic startle response) reported in the MALT animals by our group (Beesley et al, 2022).

Based on previous literature in both humans and NHPs, I have five hypotheses:

1. Compared to Controls, MALT animals would have weak AMY-PFC FC, suggesting reduced PFC top-down control on AMY reactivity, which explains the greater emotional reactivity in MALT macaques (Beesley et al., 2022).

2. Increased positive AMY-HIPP FC will be detected in MALT macaques, which will be associated with increased anxiety (startle; Beesley et al, 2022), based on previous evidence of increased emotional sensitivity (Maier et al., 2015; Fan et al., 2015).
3. Weaker HIPP-PFC FC will be detected in MALT than Control macaques, supporting the literature that emphasizes disrupted HIPP-PFC as an indicator of mental illness later in life, which often stems from early life adversity (Herringa et al, 2013; Hakamata et al., 2021).
4. AMY-HIPP-PFC FC alterations in MALT macaques will be associated with increased adult anxiety (startle).
5. Adolescent cocaine intake will not significantly affect AMY-HIPP-PFC FC.

METHODS

Subjects and Housing

Twenty-two adult rhesus monkeys (*Macaca Mulatta*) were studied as part of a larger longitudinal investigation of the effects of infant maltreatment (MALT) on brain, stress neuroendocrine, molecular, and socioemotional development from infancy to adulthood, (Howell et al., 2014, Howell et al., 2017; Morin et al., 2015; Morin et al., 2019; Morin et al.,2020; McCormack et al., 2022); see **Figure 1** for experimental timeline. Thirteen adults experienced MALT by their mothers during infancy (7 males, 6 females) and the other 9 Controls were raised by nurturing mothers (5 males, 4 females). All animals were born and raised with their mothers and families in large and complex social groups housed in outdoor/indoor compounds at the Emory National Primate Research Center (ENPRC) Field Station. Each social group had 75-150 females with their offspring, and 2-3 adult males. Water was available *ad libitum*, and animals were fed a standard low fat, high fiber monkey chow diet (Purina Lab Diets, St. Louis, MO) along with fruit and vegetables twice daily. Environmental enrichment was provided as well.

Infant Maltreatment (MALT) model, cross-fostering & collection of maternal care/MALT data

Infant MALT is spontaneously exhibited in macaque species by some mothers (Maestripieri and Carroll et al., 2000); thus, it was not experimentally induced. In this study infant MALT by the mother was defined as the co-morbid experience of physical abuse (operationalized as violent behaviors of the mother towards the infant, such as dragging, crushing, throwing, stepping or sitting on the infant) and early infant rejection (pushing away the infant or blocking contact) during the first three months of life (Maestripieri et al., 2005, Sanchez, 2006; McCormack et al., 2022). These behaviors cause pain, emotional distress and elevations in stress hormones in the infants (Drury et al., 2017; Howell et al., 2013; Maestripieri, 1998; Maestripieri & Carroll, 1998; K. McCormack et al., 2006; K. M. McCormack et al., 2022; Sanchez, 2006). Control mothers never exhibited these maltreating behaviors; instead, they showed nurturing infant care and high levels of behaviors such as cradling, grooming, ventral contact and protection (McCormack et al., 2015; McCormack et al, 2022).

Using a crossfostering experimental design and published procedures (Drury et al., 2017; Howell et al., 2017; K. M. McCormack et al., 2022), Infants were randomly assigned at birth to either a Control or a maltreating (MALT) mother to control for confounding effects of heritability and prenatal factors on maternal care effects. See **Table 1** for the counterbalanced breakdown of subjects based on foster mother group (i.e. maternal care experienced), sex, randomized crossfostering assignment, and biological mother group. All foster mothers were multiparous, and they were selected as Control or MALT based on their historical and consistent maternal care with other offspring. Social status/rank (high, middle, low) was also counterbalanced across groups to control for its potential effects on development. Mothers were not used twice in the study (i.e. biological siblings were not included in the sample in order to rule out genetic similarities). Infant focal observations that captured maternal care started the day after crossfostering and were performed during the first 3 postnatal months to measure rates of infant MALT (physical abuse, rejection) by the mother as well as other maternal behaviors and mother-infant interactions. These focal observations were performed on separate days for 30 minutes

each day (5 days/week during month 1, 2 days/week during month 2 and 1 day/week during month 3). Given that physical abuse occurs during the first 3 postnatal months with the highest rates in the first month, this protocol is optimal for early infant maltreatment documentation in this species (see McCormack et al, 2022 for details of behavioral data collection and analyses methods). Briefly, infant focal observations were collected in real time by experienced coders using an adaptation of a well-established rhesus monkey ethogram (Altmann, 1962; McCormack et al., 2006; Graves & Wallen 2006) and netbook computers with an in-house program developed at the ENPRC Behavior (Graves and Wallen, 2006) that records the behavior, actor, recipient and time for each behavior. In addition to these early adverse experiences, positive/nurturing maternal behaviors were also coded: nursing, cradling, grooming, ventral contact and protection of the infant (McCormack et al., 2022). Frequency and duration of all these behaviors were computed.

Adolescence: Cocaine Self-Administration (COC SA)

At approximately 4-5 years of age, the animals were transferred to the ENPRC Main Research Center for studies during adolescence and adulthood (**Figure 1**), where they were pair-housed with a temperature of 22 ± 2 °C, 25–50% humidity, and a 12-h light/dark cycle (lights on at 07:00 h; lights off at 19:00 h). ENPRC social enrichment protocols were followed for housing and environmental enrichment was provided on regularly. Animals were fed Purina low calory, high fiber monkey chow and supplemented with fruit and vegetables daily. Water was available *ad libitum*. After several months of acclimation, the animals underwent multiple behavioral tasks, neuroendocrine assessments, and cocaine self-administration (COC SA) as part of the extensive longitudinal study examining the long-term consequences of ELS on brain development and emotional reactivity.

The macaques underwent a cocaine (COC) i.v. self-administration (SA) study to examine whether ELS elevated the susceptibility to psychostimulant intake, reinstatement following abstinence, binging, and telescoping (i.e., accelerated progression from initiation of substance use to chronic use and

dependence) reported in human studies (Enoch 2010; Alves et al., 2020; Varghese at al., 2015; Wakeford et al., 2018; Haas et al., 2000). Subjects were trained through operant conditioning to self-administer (SA) cocaine (COC) hydrochloride dissolved in 0.9% sterile saline via i.v. catheters implanted surgically under anesthesia and aseptic conditions. The subjects were trained through a fixed ratio (FR) schedule of reinforcement where 20 lever presses (FR20) released an infusion of 0.1 mg/kg of COC. Once trained, data was acquired for different phases in the COC SA paradigm, including acquisition and maintenance of drug intake, dose-curve responses, limited access, extended access (drug escalation/binging), extinction, reinstatement and telescoping of drug SA response as described in previously published protocols (Wakeford et. al 2019, 2020). In order to control for the potential confounding effects of psychostimulant exposure on adolescent brain development, the total amount of COC intake during adolescence was calculated for each subject and was used as a covariate in the adult statistical models in this study. The animals were abstinent from the end of the adolescence COC SA studies until they received the adult brain MRI scans (no COC exposure for approx.2.5-3 years); no group, sex or group x sex differences in total adolescence COC intake were detected in the 22 included in this thesis. The macaques remained at the ENPRC Main Center until adulthood, which is the period of study for this project. All procedures and animal care followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (8th Edition 2011), AAALAC International recommendations and were approved by the Emory University Institutional Animal Care and Use Committee (IACUC). The ENPRC is fully accredited by AALAC International.

Adult brain MRI Data Acquisition, Processing & Analysis

We examined long-term functional effects of ELS on adult functional connectivity (FC) in neurocircuits important for emotional/stress regulation, including the PFC, AMY, and the HIPP using resting state functional magnetic resonance imaging (rs-fMRI). MRI scans were acquired at the ENPRC Imaging Center using a 3T Siemens Tim Trio scanner (Siemens Medical Solutions, Malvern, PA), an 8-channel phase array

knee coil and following published sequences and protocols by our group for macaque brain (Kovacs-Balint et al, 2019; Morin et al 2020; Pincus et al, 2021). Animals were scanned supine under anesthesia with the head immobilized using a custom-made head holder with ear bars and a mouthpiece to limit motion. A vitamin E capsule was taped on the right temple to mark the right brain hemisphere. Following induction of anesthesia with telazol (3.368 ± 0.01 mg/kg, intramuscular) and intubation, scans were collected under isoflurane anesthesia kept at the lowest possible level (1.00 ± 0.01% to effect, inhalation) to minimize its effects on the rs-fMRI signal. Physiological parameters were monitored throughout the scanning session using an oximeter, ECG, rectal thermistor, and blood pressure monitor. An i.v. catheter was used to administer dextrose/NaCl (0.45%) to maintain normal hydration and an MRI-compatible heating pad was used to maintain the subjects' body temperature.

Structural MRI (T1-weighted) scans were acquired for registration of the functional (rs-fMRI) data to the specific brain atlas space and delineation of the regions of interest (ROIs) anatomical borders, using a 3-dimensional (3D) magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence (TR/TE=2600/3.38ms, voxel-size=0.5mm3, isotropic, 8 averages; parallel imaging -GRAPPA: R=2).

Rs-fMRI scans acquisition and data processing: Two 15-min rs-fMRI scans were acquired using a T2*-weighted gradient echoplanar imaging (EPI) sequence (400 volumes, TR/TE = 2160/25ms, voxel size: 1.5 mm^3 isotropic) to measure FC between ROIs based on ROI-ROI temporal correlations in blood oxygen-level dependent (BOLD) signal changes. An additional reverse-phase encoding scan was acquired to unwarp distortions in the EPI scans (Andersson et al, 2003). Rs-fMRI scan acquisition and data processing were done following published protocols by our group (Kovacs-Balint et al., 2019; Morin et al, 2020; Pincus et al, 2021; Kovacs-Balint et al, 2023). Briefly, the EPI images then underwent a series of pre-processing steps to minimize noise and artifact, including (1) reverse phase-encoding distortion correction, (2) slice-time correction (which controls for the intensity differences between even and odd slices), (3) motion correction, and (4) signal normalization. After these pre-processing steps, the

subjects' averaged T1-weighted image were transformed to align with the UNC-Emory T1-weighted rhesus juvenile 12 month extended brain atlas (Shi et al., 2017) because of improved quality of results in comparison to other adult macaque brain atlases available (Kovacs-Balint et al. 2023). Further pre-processing steps include (1) functional signal detrending, (2) nuisance regressor removing, (3) temporal low-pass filtering, and (4) exclusion of any subjects with significant BOLD signal dropout and/or insufficient co-registration (Kovacs-Balint et al, 2023). For each subject, functional connectivity (FC) was analyzed between the following ROIs: AMY-PFC subregions, HIPPO-PFC subregions, AMY-HIPP, rightAMY-leftAMY, and rightHIPPO-leftHIPPO (G. Paxinos et al., 2000). ROI identification was guided by macaque brain atlases and region-specific neuroanatomical criteria; see the ROIs section below for more details. The time course of the rs-fMRI BOLD signal was averaged across the voxels within a given ROI and then correlated with the time course of another ROI. Analyzing the time course of the rs-fMRI BOLD signal between the PFC, AMY, and HIPP allows the generation of one time course correlation matrix for each subject. Using these correlation matrices, correlation coefficients (r-values) between ROIs for each subject were extracted via Matlab (MathWorks Inc, Natick, MA), which were then Fisher Z-transformed to normalize the data (e.g. Kovacs-Balint et al., 2019).

Regions of Interest (ROIs):

AMY, HIPP, and the various subregions of the PFC (dorsolateral PFC-dlPFC- Areas 9 and 46; medial/ventromedial PFC-mPFC- Areas 14, 24 -anterior cingulate: ACC-, 25 and 32; orbitofrontal cortex-OFC- Areas 11 and 13; ventrolateral PFC -vlPFC- Areas 45 and 47) were defined based on established macaque MRI anatomical parcellations (Paxinos et al., 2000) and then mapped onto the juvenile (12 months) UNC-Emory macaque brain atlas (Shi et al, 2017). These AMY, HIPP, and PFC ROIs were then manually edited based on guidance from an expert rhesus macaque neuroanatomist from Emory (Dr. J. Bachevalier) and following macaque-specific neuroanatomical landmarks (Walker 1940; Petrides and

Pandya 1994, 2002; Reding et al., 2020; Saleem 2012; Styner et al., 2007) to provide accurate anatomical definition of the ROIs. See **Figure 2 (top)** for PFC ROIs and **Figure 2 (bottom)** for AMY and HIPP ROIs.

Adult Amplitude of Startle Response

Once the animals were trained to sit in a primate chair via positive reinforcement, they were placed in the primate chair inside a ventilated, sound-attenuated startle chamber. The chair rested on a platform that translated the animal's movements in response to the startle stimulus into electrical signals that were converted into a measure of the startle response amplitude. We used an acoustic startle paradigm to measure baseline startle amplitude as an established and translational biomarker for anxiety and emotional reactivity in human and animal models (Sanchez et al., 2005; Shalev et al., 2000). Auditory stimuli of varying intensities (95dB, 100dB, 110dB, 115dB and 120dB) were administered, and the median acoustic startle amplitudes to each of them were collected following published procedures for rhesus monkeys (Kazama et al., 2013) on two testing days for each animal by another undergraduate student in the lab -Alex Beesley- (Beesley et al., 2022). I examined whether FC differences between the MALT and Control groups predicted higher anxiety during adulthood (baseline startle) reported in the MALT animals (Beesley et al, 2022).

Statistical Analysis

IBM SPSS Statistics (version 28.0.1.0; IBM Corporation, Armonk, NY) was used to perform all statistical analysis with statistical significance level set at $p \leq 0.05$. Mean±standard error of the mean (SEM) was used to summarize variables and visualize trends and effect sizes were calculated as $\eta p2$. Because the analysis of variance (ANOVA) and covariance (ANCOVA) assume the data is normally distributed and there is homogeneity of variances, the Shapiro-Wilk and Levene tests were used to check for normality and homogeneity of variances, respectively. Due to ROI-ROI FC data ranging from -1 to 1 (i.e. correlation -r- values), FC data that violated normality could not be log10-transformed, and it is reported using the Greenhouse-Geisser corrected values to be conservative. Additionally, since the repeated measure

(Laterality) in the ANOVAs and ANCOVAs only had two levels (Left, Right), the Mauchly's test of sphericity could not be run and the Greenhouse-Geisser corrected values for sphericity not-assumed are reported.

A Two-Way ANOVA was conducted to analyze the main and interaction effects of Group (MALT, Control) and Sex (Male, Female) as fixed factors on FC between Left AMY-Right AMY and between Left HIPP-Right HIPP. Repeated measures (RM) ANOVA was used to assess the effects of Group and Sex as fixed factors and brain Laterality (Left, Right) as the RM factor on FC between AMY-PFC, HPP-AMY, and HIPP-PFC regions. To assess whether anesthesia (Telazol and/or isoflurane -ISO-) affected the FC results, the ANCOVAs and RM ANCOVAs were re-run with the same fixed and RM factors, although adding Telazol and ISO as covariates. If these ANCOVAs or RM ANCOVAs yielded significant main or interaction effects of the telazol or ISO covariates, they were re-run adding Lifetime Cocaine intake as a covariate to control for the potential long-term effects of COC adolescence exposure on circuits FC. When the ANCOVA or RM ANCOVA models that included Telazol and ISO as covariates did not yield significant main or interaction effects of the covariates, Lifetime Cocaine Intake was added as a covariate to the original ANOVA (or RM ANOVA) without anesthetic covariates. For the few ROI-ROI FC data with extreme signal dropout outliers, the statistical models above were re-run without the outliers to examine whether they drove the effects. Although the statistical significance level was set at $p \leq 0.05$, trends are also reported in Results (defined as $0.05 < p < 0.1$). Bar charts in Figures are presented for Control and MALT groups collapsed across males and females, unless significant main or interaction effects of Sex (or trends) were detected.

Although it would have been important to control for heritable/prenatal factors by including Biological mother (either Control or MALT) as factor or covariate in the statistical models, the study is underpowered to examine its potential effect due to the small sample size.

When significant Group effects were detected, Pearson (or Spearman-Rank, when data was not normally distributed) correlations were used to examine associations between adult FC data and startle measures. When significant effects of COC as a covariate were detected in the ANOVA (or ANCOVA) models, Pearson (or Spearman-Rank, when data was not normally distributed) correlations were used to examine the directionality of associations between adolescent COC exposure and adult FC measures.

RESULTS:

Amygdala (AMY) functional connectivity (FC)

Left AMY-Right AMY FC:

Left AMY-Right AMY FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The Two-Way ANOVA with Group and Sex as fixed factors found no significant main or interaction effects, although there was a trend towards significance for main Sex effects ($F(1,22) = 4.121$, $p = 0.057$, $\eta p2 = 0.186$). Visual inspection of **Figure 3** indicates stronger FC in males than females, with a suggestive weaker FC in MALT than Control females. When this model was re-run as a Two-Way ANCOVA adding Telazol and ISO as covariates, no significant effects of the covariate were detected; therefore, they were dropped from the model, and the Two-Way ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, which made the main effects of Sex significant ($F(1,22) = 5.053$, $p = 0.038$, $\eta p2 = 0.229$), and detected a trend towards significance for a Lifetime Cocaine Intake effect ($F(1,22) = 4.244$, $p = 0.055$, $\eta p2 = 0.200$). No other main or interaction effects were detected.

AMY-mPFC FC:

AMY-Area 14

AMY-Area 14 FC data were normally distributed based on the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and

Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. Visual inspection of data in **Figure 4** indicates that although the group average FC between Amy and Area 14 is close to zero, it is driven by a split distribution of subjects with positive and negative FC within each group, which highlights an interesting individual variability. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no significant effects of the covariates were detected; therefore, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality or covariate effects detected. Finally, excluding the four outliers with high signal dropout in Area 14 had no effect on the results.

AMY-Area 24

AMY-Area 24 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. Visual inspection of the data in **Figure 5** also shows a split distribution of subjects with positive and negative FC within each group. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariates effects were detected; therefore, they were dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality or covariate effects detected.

AMY-Area 25

AMY-Area 25 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. Visual inspection of the data in **Figure 6** shows a split distribution of subjects with positive and negative FC within each group, highlighting high individual variability. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariate effects were detected; therefore they were

dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake, instead, as a covariate, with no Group, Sex, Laterality or covariate effects detected.

AMY-Area 32

AMY-Area 32 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. Visual inspection of the data in **Figure 7** indicates a split distribution of subjects with positive and negative FC within each group, highlighting great individual variability. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no effects of the covariates were detected; therefore, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality or covariate effects detected.

<u>AMY-OFC FC:</u>

AMY-Area 11

AMY-Area 11 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no Group, Sex or Laterality main or interaction effects. **Figure 8** also suggests split of subjects with negative versus positive FC in both MALT and Control groups. When the model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Laterality emerged ($F(1,22) = 4.688$, $p = 0.046$, $\eta p2 = 0.227$), and a trend towards significance of an interaction effect of Laterality* ISO ($F(1,22) = 3.977$, $p = 0.063$, $\eta p2 = 0.199$) was detected. Due to the lack of significant effects of the anesthesia covariates, they were dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality main or covariate effects detected.

AMY-Area 13

AMY-Area 13 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no Group, Sex or Laterality main or interaction effects. **Figure 9** shows high individual variability with a split distribution of subjects with positive versus negative FC within each group. When the model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, a trend towards significance of an interaction effect of Laterality * Telazol ($F(1,22) = 4.305$, $p = 0.055$, $\eta p2 = 0.212$) was detected. Due to the lack of significant effects of the anesthesia covariates, they were dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality main or covariate effects detected.

AMY-dlPFC FC:

AMY-Area 9

AMY-Area 9 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. **Figure 10** also shows a split distribution of subjects with positive versus negative FC within each group. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariates effects were detected; thus, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality main or covariates effects detected. Finally, excluding the one outlier with high signal dropout in Area 9 had no effect on the results.

AMY-Area 45

AMY-Area 45 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects.

Figure 11 shows a split distribution of subjects with positive versus negative FC within each group in the left hemisphere, but mainly a negative FC in the right, despite no significant laterality effects. When the model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no effects of the anesthesia covariates were detected; thus, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, with no Group, Sex, Laterality or covariate effects detected. Finally, excluding the two outliers with high signal dropout in Area 45 had no effect on the results.

AMY-Area 46

AMY-Area 46 FC data, specifically left Area 46, were not normally distributed according to the Shapiro-Wilks test but passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. Although most group FC averages in **Figure 12** are negative, the data show individual variability with several positive FCs within each group. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariates effects were detected; thus, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality or covariate effects detected. Finally, excluding the three outliers with high signal dropout in Area 46 had no effect on the results.

<u>AMY-vlPFC:</u>

AMY-Area 47

AMY-Area 47 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. **Figure 13A** shows a split distribution of subjects with positive versus negative FC within each group. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariates

effects were detected; thus, they were dropped from the model and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, where main effects of Laterality ($F(1,22) = 11.284$, $p = 0.004$, $\eta p2 = 0.399$), and Lifetime Cocaine Intake ($F(1,22) = 4.697$, $p = 0.045$, $\eta p2 = 0.216$), as well as an interaction effect of Laterality * Lifetime Cocaine Intake ($F(1,22) = 8.104$, $p = 0.011$, $\eta p2 = 0.323$) were detected. Thus, to explore how Lifetime Cocaine intake affected AMY-Area 47 FC measures, a Pearson correlation was run and showed a significant positive correlation between COC intake and AMY- left Area 47 FC ($r=0.582$, $p=0.004$), indicating that the macaques who consumed greater amounts of cocaine overall exhibited higher positive AMY-left AMY 47 FC (**Figure 13B**). No significant correlation was detected between COC intake and AMY-right Area 47 FC. No other Group, Sex, Laterality or covariate effects were detected. Finally, excluding the one outlier with high signal dropout in Area 47 had no effect on the results.

HIPPOCAMPUS (HIPP) FUNCTIONAL CONNECTIVITY

HIPP-AMY FC:

HIPP-AMY FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The Two-Way ANOVA with Group and Sex as fixed factors found no significant main or interaction effects. The data in **Figure 14** show mainly positive FC in all animals. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a trend towards significance of a main effect of Telazol ($F(1,22) = 4.069$, $p = 0.061$, $\eta p2 = 0.203$) was detected. Due to the lack of significant effects of the anesthesia covariates, they were dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with no Group, Sex, Laterality or covariate effects detected.

HIPP-mPFC FC:

HIPP-Area 14

HIPP-Area 14 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. The data in **Figure 15** show mainly negative FC in all animals. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of ISO ($F(1,22) = 7.156$, $p = 0.017$, $\eta p2 = 0.309$) was detected, and Group and Sex effects did not change. Since there was a significant effect of anesthesia (ISO), ISO and Telazol were included in the RM ANCOVA along with Lifetime Cocaine Intake as an additional covariate, and the main effect of ISO remained ($F(1,22) = 6.645$, $p = 0.021$, $\eta p2 = 0.307$). Finally, excluding the three outliers with high signal dropout in Area 14 had no effect on the results.

HIPP-Area 24

HIPP-Area 24 FC data were not normally distributed according to the Shapiro-Wilks test but passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found a main effect of Sex ($F(1,22)= 10.036$, $p=0.005$, $\eta p2 = 0.358$). **Figure 16** indicates a strong negative FCs in the females, while the males have weak positive and negative FCs. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Sex ($F(1,22) = 7.386$, $p = 0.015$, $\eta p2 = 0.316$) remained, and significant main effects of Telazol ($F(1,22) = 5.554$, $p = 0.032$, $\eta p2 = 0.258$) and ISO ($F(1,22) = 5.998$, $p = 0.026$, $\eta p2 = 0.273$) were detected. Since there was a significant effect of anesthesia, ISO and Telazol were included in the RM ANCOVA along with Lifetime Cocaine Intake as an additional covariate, and significant main effects of Telazol ($F(1,22) = 5.392$, $p = 0.035$, $\eta p2 = 0.264$), ISO ($F(1,22) = 5.583$, $p = 0.032$, $\eta p2 = 0.271$), and Sex ($F(1,22) = 6.992$, $p = 0.018$, $\eta p2 = 0.318$) remained. No other Group, Sex, Laterality main or interaction effects or covariates effects were detected.

HIPP-Area 25

HIPP-Area 25 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found a main effect of Sex ($F(1,22) = 12.714$, $p = 0.002$, $\eta p2 = 0.414$). **Figure 17** indicates a strong negative FC in the females, while the males have weak positive and negative FCs. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Sex ($F(1,22) = 9.308$, $p = 0.008$, $\eta p2 = 0.368$) remained, and no other main or interaction effects were detected. When this model was re-run as a RM ANCOVA adding Telazol and ISO as covariates, no covariates effects were detected; therefore, they were dropped from the model, and the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, instead, with the main effect of Sex ($F(1,22) = 13.111$, $p = 0.002$, $\eta p2 = 0.435$) that still remained, and no other main or interaction effects were detected.

HIPP-Area 32

HIPP-Area 32 FC data were not normally distributed according to the Shapiro-Wilks test but passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. **Figure 18** indicates a split distribution of subjects with positive and negative FCs within each group. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Telazol ($F(1,22) = 9.098$, $p = 0.008$, $\eta p2 = 0.363$) and a main effect of ISO ($F(1,22) = 6.130$, $p = 0.025$, $\eta p2 = 0.277$) were detected, and Group and Sex effects did not change. Since there was a significant effect of anesthesia, ISO and Telazol were included in the RM ANCOVA along with Lifetime Cocaine Intake as an additional covariate, and significant main effect of Telazol ($F(1,22) = 8.902$, $p = 0.009$, $\eta p2 = 0.372$) and a main effect of ISO ($F(1,22) = 5.731$, $p = 0.030$, $\eta p2 = 0.276$) remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

<u>HIPP-OFC FC:</u>

HIPP-Area 11

HIPP-Area 11 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant Group, Sex or Laterality main or interaction effects. **Figure 19** indicates a bias towards a negative FC in the Control animals, and in the MALT animals, a split distribution of subjects with positive and negative FCs is exhibited. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Telazol ($F(1,22) = 5.452$, $p = 0.033$, $\eta p2 = 0.254$) and a main effect of ISO ($F(1,22) = 12.436$, $p = 0.003$, $\eta p2 = 0.437$) emerged, without affecting the Group or Sex effects. Since there was a significant effect of anesthesia, ISO and Telazol were included in the RM ANCOVA along with Lifetime Cocaine Intake as an additional covariate, and significant main effects of Telazol ($F(1,22) = 5.431$, $p = 0.034$, $\eta p2 = 0.266$) and of ISO ($F(1,22) = 11.831$, $p = 0.004$, $\eta p2 = 0.441$) remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

HIPP-Area 13

HIPP-Area 13 FC data were normally distributed according to the Shapiro-Wilks test but did not pass the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found a main effect of Sex ($F(1,22) = 7.861$, $p = 0.012$, $\eta p2 = 0.304$). **Figure 20** indicates a negative FC in the females, while the males also exhibit a negative FC with the exception of the MALT males in the left hemisphere. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Sex ($F(1,22) = 6.913$, $p = 0.018$, $\eta p2 = 0.302$) remained. Thus, due to the lack of effects of the anesthesia covariates, they were dropped from the model. When the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, a main effect of Sex ($F(1,22) = 7.415$, $p = 0.014$, $\eta p2 = 0.304$) still remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

HIPP-dlPFC FC:

HIPP-Area 9

HIPP-Area 9 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found an interaction effect of Group *Sex ((F(1,22) = 5.365 , p = 0.033, ηp2 = 0.230). **Figure 21** indicates that while Control females exhibited a stronger negative FC than the MALT females, the Control males showed a weaker positive FC compared to MALT males. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Laterality (F(1,22) = 6.761, p = 0.019, ηp2 = 0.297) , an interaction effect of Laterality * Telazol (F(1,22) = 5.860, p = 0.028, ηp2 = 0.286), an interaction effect of Laterality * ISO (F(1,22) = 4.863 , p = 0.042, ηp2 = 0.233), and a trend towards significance of an interaction effect of Group * Sex (F(1,22) = 3.925 , p = 0.065, ηp2 = 0.197) were detected. No significant correlation was detected between startle measures and HIPP- Area 9 FC. Since there were significant effects of anesthesia, ISO and Telazol were included in the RM ANCOVA along with Lifetime Cocaine Intake as an additional covariate, and a main effect of Laterality (F(1,22) = 6.641, p= 0.021, ηp2 = 0.307), an interaction effect of Laterality * Telazol (F(1,22) = 5.803 , p=0.029, ηp2 = 0.279), and an interaction effect of Laterality * ISO (F(1,22) = 4.545, p= 0.050, ηp2 = 0.233) remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

Finally, excluding the one outlier with high signal dropout in Area 9 altered the results. In the RM ANCOVA with Telazol and ISO as covariates, the interaction effects between Laterality * Telazol and Laterality * ISO were not maintained. In the RM ANCOVA with Telazol, ISO, and Lifetime Cocaine Intake as covariates, the Laterality * ISO interaction effect was not maintained, and the Laterality * Telazol interaction effect no longer was significant but instead was trending towards significance (F(1,21) = 3.525 , p= 0.081, ηp2 = 0.201). All other main and interaction effects remained.

HIPP-Area 45

HIPP-Area 45 FC data were normally distributed according to the Shapiro-Wilks test and passed the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found an interaction effect of Group * Sex * Laterality ($F(1,22) = 5.703$, $p = 0.028$, $\eta p2 = 0.241$) and a trend towards significance of interaction effect of Laterality * Sex ($F(1,22) = 4.234$, $p = 0.054$, $\eta p2 = 0.190$). **Figure 22** shows that the females display a stronger negative FC than the males in most groups. No significant correlation was detected between startle measures and HIPP-Area 45 FC. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, the Group * Sex * Laterality interaction effect remained ($F(1,22) = 5.620$, $p = 0.031$, $\eta p2 = 0.260$) Due to the lack of effects of the anesthesia covariates, they were dropped from the model. When the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, an interaction effect of Laterality * Sex interaction effect emerged ($F(1,22) = 4.540$, $p = 0.048$, $\eta p2 = 0.211$) but the trend towards significance of an interaction effect of Group * Sex *Laterality effect was not significant anymore, although there was a trend towards significance ($F(1,22) = 4.412$, $p = 0.051$, $\eta p2 = 0.206$) remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

Excluding the two outliers with high signal dropout in Area 45 did alter the results. Instead of maintaining the Laterality * Group* Sex interaction effect, the RM ANOVA detected a trend towards significance of a Laterality * Group * Sex interaction effect ($F(1,18)= 3.546$, $p=0.081$, $\eta p2 = 0.202$), suggesting the outliers may be driving the interaction effect. Similarly, the RM ANCOVA with Telazol and ISO as covariates also detected a trend towards significance of the Group*Sex * Laterality interaction effect ($F(1,18)= 4.680$, $p=0.051$, $\eta p2 = 0.281$) as well as a trend towards significance of an interaction effect of Laterality * Telazol Dose ($F (1,18)=4.005$, $p=0.069$, $\eta p2 = 0.250$). Additionally, when cocaine was added to the model as a covariate, the Group the RM ANCOVA with Lifetime Cocaine as a covariate did not detect any significant main or interaction effects of Group, Sex, Laterality, or the covariate.

HIPP-Area 46

HIPP-Area 46 FC data were normally distributed according to the Shapiro-Wilks test but did not pass the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found a main effect of Sex ($F(1,22) = 9.692$, $p = 0.006$, $\eta p2 = 0.350$). **Figure 23** indicates mostly strong negative FC in the females, while the males have weak positive and negative FCs. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Sex ($F(1,22) = 6.343$, $p = 0.023$, $\eta p2 = 0.284$) remained. Due to the lack of effects of the anesthesia covariates, they were dropped from the model. When the RM ANCOVA was run adding Lifetime Cocaine Intake as a covariate, a main effect of Sex ($F(1,22) = 9.493$, $p = 0.007$ $\eta p2 = 0.358$) still remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

Excluding the three outliers with high signal dropout in Area 46 did alter the results. Interestingly, when Telazol and ISO were added to the RM ANCOVA as covariates, instead of a main effect of Sex, a trend towards a main effect of Sex was detected $F(1,22)= 4.080$, $p=0.063$, $\eta p2 = 0.226$). In contrast, when the RM ANCOVA was run with solely Lifetime Cocaine as a covariate, a main effect of Sex ($F(1,22)=7.776$, $p=0.014$, $\eta p2 = 0.341$) emerged again. All other main and interaction effects remained.

<u>HIPP-vlPFC:</u>

HIPP-Area 47

HIPP-Area 47 FC data were not normally distributed according to the Shapiro-Wilks test and did not pass the Levene's test for homogeneity of variances. The RM ANOVA with Group and Sex as fixed factors and Laterality as the RM factor found no significant main or interaction effects of Group, Sex, or Laterality. **Figure 24** indicates a split distribution of subjects with positive and negative FCs within each group. When this model was run as a RM ANCOVA adding Telazol and ISO as covariates, a main effect of Telazol ($F(1,22) = 4.693$, $p = 0.046$, $\eta p2 = 0.227$) emerged, without changing the Group or Sex effects. Since there were significant effects of anesthesia, ISO and Telazol were included in the RM ANCOVA along

with Lifetime Cocaine Intake as an additional covariate, a main effect of Telazol ($F(1,22) = 5.112$, $p = 0.039$, $\eta p2 = 0.254$) remained. No other Group, Sex, Laterality main or interaction effects or covariates effect were detected.

Excluding the one outlier with high signal dropout in Area 47 did alter the results. Interestingly, when Telazol and ISO were added to the RM ANCOVA as covariates, instead of a main effect of Telazol, a trend towards significance of a main effect of Telazol ($F (1,20) = 4.188$, $p=0.060$, and $\eta p2 = 0.230$) was detected; thus, the outlier may be driving the main effect of Telazol. When the RM ANCOVA was run with solely Lifetime Cocaine as a covariate, no Group, Sex, Laterality main or interaction effects or covariates effect were detected.

DISCUSSION:

This study examined the long-term effects of infant maltreatment (MALT), a form of early life stress (ELS), on adult functional connectivity (FC) between the amygdala (AMY), hippocampus (HIPP), and subregions of the prefrontal cortex (PFC) -mPFC, OFC, dlPFC, and vlPFC- due to the critical role of these circuits in emotional and stress regulation. For this, brain resting state functional MRI (rs-fMRI) scans were collected to examine ROI-ROI FC (AMY-AMY, AMY-PFC, AMY-HIPP, and HIPP-PFC). Our lab has previously reported greater anxiety in adult MALT animals using a measure of baseline amplitude of the acoustic startle reflex (Beesley et al, 2022), and the goal of this thesis was to identify alterations in PFC-AMY-HIPP FC that could underlie those effects. In addition, total COC intake during adolescence was added as a covariate to the statistical models to control for its potential developmental impact on FC in these cortico-limbic circuits during adolescence. The findings suggest that contrary to the hypotheses, infant MALT did not have long-term effects on adult AMY FC (AMY-AMY, AMY-PFC, and AMY-HIPP). The results also contrast with a previous publication from this cohort of animals studied from infancy to the juvenile, prepubertal, period (at 3, 6, 12 and 18 months of age), where weaker AMY-PFC FC was found in MALT than Control animals across development, particularly between AMY and subgenual cingulate (Area 25) anterior cingulate (Area 24), Area 13 in the OFC and Area 9 in the dlPFC, whereas left AMY-right AMY FC was stronger in MALT than Controls (Morin et al, 2020). The findings in this thesis suggest transient effects of MALT on AMY FC during infancy and the juvenile period, with recovery ("catch up") of AMY-AMY and AMY-PFC typical FC underlying emotional regulation by adulthood. On the other hand, this study revealed long-term effects of MALT in HIPP-PFC FC, specifically between HIPP-Area 9 (dlPFC) and HIPP-Area 45 (vlPFC), and in both cases different in males than females; specifically, MALT females showed weaker negative FC than Control females, whereas the opposite directionality was observed in males. Adult anxiety was not associated with FC between HIPP and these two lateral PFC regions, suggesting functional alterations in other emotional regulation circuits that could underlie the

exaggerated startle amplitude in the animals with ELS. Additional effects of Sex and Laterality were detected in the FC of AMY, PFC and HIPP circuits. Surprisingly, we did find a significant positive correlation between adolescence COC intake and AMY FC with vlPFC Area 47 FC , which is interesting given the vlPFC role in reward and reappraisal of addictive stimuli. Overall, these findings suggest long-term effects of infant MALT on specific HIPP-PFC circuit FC, but not AMY FC of adult rhesus monkeys, which contrasts with the weaker AMY-PFC FC reported in MALT animals compared to Controls during infancy and the juvenile period; this indicates that some effects of infant MALT on these corticolimbic functional development are temporary/transient, while others are long-term.

Effects of MALT on ROI-ROI FC:

The findings suggest that contrary to the hypotheses, infant MALT did not have a long-term effect on adult AMY FC (AMY-AMY, AMY-PFC, or AMY-HIPP). The AMY-PFC FC studied involved subregions in the mPFC (Areas 14, 24 -anterior cingulate cortex-, 25 -subgenual cingulate- and 32), OFC (Areas 11 and 13), and dlPFC (Areas 9 and 46) and vlPFC (Areas 45 and 47). The different PFC subregions were selected based on different connectivity with the AMY and functional roles in emotional/stress regulation, cognitive/executive function, goal-directed behavior (Arnsten, 2009; Tottenham & Sheridan, 2010; Morgan et al., 1993; Phelps et al., 2004; Sotres-Bayon et al., 2006; Rauch et al., 2006; Milad and Quirk et al., 2002; Roy et al., 2012; Gusnard et al., 2001; Lane et al., 1977; Zwanzger et al., 2014; Notzon et al., 2017; Wager et al., 2008; Hui et al., 2022) as well as previous findings of PFC region-specific AMY FC effects of infant MALT in this cohort of animals from infancy through the juvenile period (Morin et al, 2020). Morin and colleagues found weaker AMY-PFC FC in MALT than Controls from 3-18 months of age between AMY and mPFC Areas 24 and 25, Area 13 in the OFC and Area 9 in the dlPFC; on the other hand, left AMY-right AMY FC was stronger in MALT than Control animals. Those results were interpreted as supporting evidence that early life adversity leads to disruption of the PFC top-down inhibition of the AMY, which can explain AMY hyperactivity and, thus, greater fear and anxiety, consistent with other

reports in humans (Morin et al., 2020; Pagliaccio et al., 2015; Guadagno et al., 2021). My results suggest that, contrary to the original hypothesis, infant MALT did not have a long-term effect on adult AMY FC (AMY-AMY, AMY-PFC or AMY-HIPP). The adult findings indicate transient effects of MALT on AMY FC during infancy and the juvenile period, with recovery ("catch up") of AMY-AMY and AMY-PFC typical FC underlying emotional regulation by adulthood. This hints at the potential ability and resilience of the corticolimbic neurocircuitry to adjust and recover from the weak AMY-PFC FC observed the younger stages of development as life goes on. Even though the MALT macaques did not show significant differences in AMY-PFC FC from the Controls during adolescence and adulthood, they still exhibited elevated state anxiety and increased cortisol levels (Morin et al., 2019; Beesley et al., 2022), suggesting alterations in other neurocircuits that play a role in emotional and stress regulation, including FC alterations reported in amygdala-insula-anterior cingulate cortex circuitry in MALT individuals (Pang et al., 2022; Thomason et al., 2015).

Studies in humans consistently report lasting impacts of child MALT on adolescent and adult AMY-AMY and AMY-PFC FC (Jedd et al., 2015; Gee et al., 2013; Birn et al., 2014), which is associated with psychopathology. One speculation as to why humans experience more pervasive effects of MALT on AMY FC could be the experience of revictimization in humans, which is the increased risk of individuals with child MALT experiences to bullying and physical or sexual abuse later in life, including as adults (Messman et al., 1996). Evidence from the literature highlights how adults who have suffered childhood trauma are more vulnerable to psychopathologies, such as depression, anxiety, and stress disorders, via revictimization and concurrent trauma, and exhibit altered patterns of FC in the amygdala, prefrontal cortex, and hippocampus (Hong et al., 2023; McIver et al., 2019). In contrast, infant MALT in this NHP model is limited to the first 3-6 months of age (equivalent to the first 2 years in humans) without apparent revictimization which may allow for more recovery after the ELA experience. Additionally, we need to consider the potential interaction of neurodevelopmental effects of infant

MALT with the remodeling effects of puberty and increases in gonadal hormones (estradiol, progesterone -P- and testosterone -T-) on AMY-PFC FC during adolescence, which is critical for proper emotional regulation (Van Wingen et al., 2011). These authors report sometimes opposite effects of gonadal hormones increases in males and females (e.g. P seems to enhance the negative AMY-mPFC coupling in females; T is inversely associated with the strength of the negative AMY-OFC coupling in males and females), suggesting that increases in gonadal hormones during puberty could have interacted with effects of infant MALT on FC of cortico-limbic circuits, resulting in different effects in males versus females, impacting emotional control and adult anxiety differentially in both groups and sexes.

In disagreement with our second hypothesis, our data mostly show a bias towards positive AMY-HIPP FC in both the Control and MALT macaques with several MALT macaques showing negative AMY-HIPP FC relative to Controls. De Voogd et al., 2017 stresses that positive AMY-HIPP FC is facilitates in strengthening of memory; thus, the positive AMY-HIPP FC in juvenile and adult macaques, independent of Control/MALT, may indicate typical memory enhancements associated with emerging adulthood. There is a lack of literature that explains the significance of a negative AMY-HIPP FC, particularly its association with childhood maltreatment, but existing studies elaborate on significance of negative AMY-HIPP FC in other forms of stress. Barch et al., 2016 reports early life adversity, in the form of poverty, in 3-5 year old children were strongly associated with weakened negative AMY-HIPP resting state FC, which was found to be predictive of depression later in life. St. Jacques et al., 2009 stresses that relative to young adults, older adults exhibit decreased AMY-HIPP FC in response to recalling negative memories, supporting the finding of reduction in memory for negative stimuli with age. Thus, there is tremendous variability in AMY-HIPP FC as it is dependent on the characteristics sample of participants being tested, and more research is needed to assess the question of why multiple MALT animals displayed weak negative AMY-HIPP FC.

On the other hand, this study revealed long-term effects of MALT in HIPP-PFC FC, specifically between HIPP-Area 9 and HIPP-Area 45, both regions part of the lateral PFC, and in both cases different in males than females; specifically, MALT females show weaker negative FC than Control females, whereas the opposite directionality was observed in males. Adult anxiety was not associated with FC between HIPP and these two lateral PFC regions, suggesting functional alterations in other emotional regulation circuits responsible for the exaggerated startle amplitude in the animals with ELS. Regarding our third hypothesis, our data support the third hypothesis as we found effects of MALT on HIPP-PFC FC. Similar to AMY-PFC, HIPP-PFC also exhibits a split distribution of adult subjects with positive and negative FC within the MALT and Control groups, suggesting that FC within corticolimbic neurocircuitry may be regulated by other neurobiological or environmental factors and is independent of early life stress. An interaction effect between Group (MALT vs Control) and Sex was found on the FC of HIPP-Area 9 of the dlPFC in which stronger negative FC is seen in Control females relative to MALT females as well as in MALT males relative to Control males. Additionally, we detected a Group * Sex* Laterality interaction effect in the HIPP-Area 45 of the frontal eye field, which is intriguing as we speculate that depending on the hemisphere of the brain (left vs right) and the sex, the effects of MALT on HIPP-Area 45 FC are altered. Alterations in HIPP-Area 9 and HIPP-Area 45 FC were not associated with adult STARTLE amplitudes (a translational measure of adult anxiety), suggesting that the higher anxiety in MALT than Control adults may have its origin in different emotional regulatory circuits and that the FC differences between MALT and Control animals in HIPP-Area 9 and HIPP-Area 45 may underlie other negative outcomes observed in MALT individuals, such as deficits in executive functions, particularly in working memory (Chen et al., 2017) and other cognitive impairments (Yoon et al, 2008; Bahner et al., 2015).

Comparing our effects of MALT on ROI-ROI FC with the findings in the literature in humans, we find that in contrast to this study, adults who experienced MALT experience weaker PFC-AMY FC, which

supposedly suggests suppressed or weak top-down regulation of the AMY by the PFC, leading to the AMY hyperactivity and thus greater emotional reactivity in MALT adults (Park et al., 2018; Birn et al., 2014; Fan et al., 2014). While the literature reports greater positive AMY-HIPP FC in MALT individuals, which is postulated to enhance emotional memories and upregulate the fear response (de Voogd et al., 2017; Dolcos et al., 2005; Maier et al., 2015; Fan et al., 2015), we found no effects of infant MALT on AMY-HIPP FC. Lastly, we found effects of MALT on HIPP-PFC FC, but only in the lateral PFC regions (Areas 9 and 45), with MALT females showing weaker negative or slightly positive HIPP-PFC FC than control females, consistent with the literature (Herringa et al, 2013; Hakamata et al., 2021) and suggesting impaired executive emotional modulation in MALT females. In males, we found the opposite (stronger negative HIPP-PFC FC in MALT males compared to control males). These opposite sex effects are interesting considering that both Herringa et al., 2013 and Hakamata et al., 2021 report weaker PFC-HIPP FC in both maltreated males and females relative to non-maltreated individuals in humans.

Effects of Sex and Laterality on ROI-ROI FC:

Abundant sex effects were observed, including in (1) Left AMY-Right AMY FC, with stronger positive FC in males than the females; and (2) in HIPP FC with mPFC Areas 24 and 25, OFC Area 13, and dlPFC Area 46, with females in both Control and MALT groups displaying stronger negative FC than males. The main effects of sex on FC are not abundant in the literature, but various FC analyses have demonstrated differences in males vs females with laterality differences, as well (Zhang et al., 2016; Bluhm et al., 2008; Tian et al., 2011; Gong et al., 2011). Filippi et al., 2012 reported that while men displayed increased FC between sensorimotor and cognitive networks, women showed increased FC between attention and right working-memory networks. Kilpatrick et al., 2006 assessed how patterns of AMY FC varied based on sex using seed-voxel partial least square analysis, which examined the FC between the target region (AMY) and the whole brain and found that right AMY FC was stronger in men,

while the left AMY FC was more robust in women. Interestingly, the regions of the brain that showed stronger FC with the right AMY in males (pulvinar, striatum, sensorimotor cortex), differed from the regions of the brain that showed stronger FC with the left AMY in females (hypothalamus and subgenual cortex). In our study, HIPP-Area 45 FC exhibited a significant laterality * sex interaction effect, suggesting that alterations in HIPP-Area 45 FC may be explained by sex and laterality in conjugation.

Several main laterality effects were found in AMY-Area 11, AMY-Area 47, and HIPP-Area 9, suggesting that only particular subregions of the OFC and lateral PFC exhibit hemispheric effects in FC with the AMY and HIPP. As with sex differences, laterality effects on ROI-ROI FC demonstrate high variability across studies and the functional interpretations in the literature are inconclusive as a sum. In Strawn et al., 2012, when adolescents with generalized anxiety disorder and matched controls underwent an fMRI scan while viewing neutral and emotional images, the individuals with GAD showed decreased FC between the right vlPFC (Area 47) and mPFC (Areas 10, 24 and 32) relative to controls, but no significant difference between GAD adolescents vs controls is reported in left vlPFC-mPFC FC. This study highlights how lateralization of ROI-ROI FC is difficult to explain as it may be dependent on a multitude of factors, including the fMRI task, clinical populations studies, demographics, and social and environmental variables including exposure to early life adversity.

Limitations & Future Studies:

This study has a few limitations. Due to the small sample size (N=22), our data faced increased margins of error and reduced statistical power, which hinders the ability to detect significant effects, particularly for interactions between factors. While human studies have larger sample sizes, smaller sample sizes are commonly employed in NHP research due to the ability to control for typical confounding factors, such as diet, environment, and drug use. For studies with small sample sizes, we need to consider not just the p value, but the effect sizes, which were large (>0.14) for all significant main and interaction effects reported in this study (ranging from $\eta p2 = 0.216$ to $\eta p2 = 0.441$), suggesting

that the significant FC differences between groups are significantly different even after taking into account variability (National University 2023). Interestingly, even for effects with trends towards significance ($0.05<p<1$), the effect sizes were still large, ranging from $\eta p2 = 0.186$ to $\eta p2 = 0.212$. This implies that given a bigger sample size, these findings may reach significance.

In addition, this study was underpowered to examine the effects of biological mother and cross-fostering, which should be incorporated into the statistical models as covariates in future studies with larger sample size; several studies in rodents and NHPs show a significant effect of cross-fostering, particularly the postnatal maternal environment, on brain development and emotional behavior during adulthood (Lu et al., 2009; McCarty et al., 2017; A.Bartolomucci et al., 2004; Maestripieri 2005; Kinnally et al., 2018). Other studies demonstrate how cross-fostered individuals and biologically reared individuals show no significant differences in other behavioral phenotypes later in life, such as resistance to prenatal relocation stress (Ceniceros et al., 2021) or production of food-call vocalizations (Owren et al., 1993; Cheney et al., 1992), revealing that the effects of cross-fostering on adult behavioral outcomes are dependent on the type of behavior analyzed as well as individual differences in maternal care.

Surprisingly, we found a significant positive correlation between adolescence COC intake and AMY FC with dlPFC Area 47 FC, which is interesting, given the vlPFC role in reward and reappraisal of addictive stimuli (Fisher et al., 2010; Zilverstand et al., 2017). Verdejo-Garcia et al., 2015 shows how relative to controls, cocaine users displayed weak vlPFC signal during a reversal learning task, in which participants had to choose the correct stimulus between two stimuli according to variable predetermined rules, under fMRI. Cocaine users were more error-prone during the task, suggesting that cocaine consumption impedes neural activity in the vlPFC, which then hindered behavioral modification and reappraisal processes. In relation to our findings, we detected a positive association between the AMY-Area 47 FC and lifetime cocaine intake, indicating that macaques who consumed greater amounts of cocaine exhibited positive AMY-Area 47 FC, which is considered to be a biomarker for altered network

function and deficits in emotional regulation as shown in previous literature (Hafeman et al., 2017; Townsend et al., 2013; Wen et al., 2023). We speculate that the positive AMY-Area 47 FC in the macaques who consumed more cocaine is driven by diminished activity in the vlPFC, which translates to AMY hyperactivity due to reduced top-down inhibition from the PFC towards the AMY and thus increased susceptibility to cocaine intake.

Furthermore, the significant effects of anesthesia (Telazol and ISO) on FC between HIPP and PFC suggests that ISO and Telazol affect the neural activity in the HIPP and PFC, which in turn affects the functional coupling between the two ROIs. Previous literature supports how Telazol and ISO can affect brain activation, specifically FC patterns in rodents and NHPs (Grandjean et al., 2014; Kovacs-Balint et al., 2019; Bonhomme et al., 2011). Typically, anesthesia is known to dampen neural activity in the PFC and the HIPP and thus weakensFC between the two ROIs (Vedaei et al., 2022; Botovas et al., 2010). Our data most likely incurred a reduction of FC between HIPP-PFC driven by anesthesia, and future studies should test for the effects of lifetime cocaine intake as a fixed factor on the adult HIPP-PFC FC.

Additionally, due to the lack of directionality information in the rs-fMRI data, we are unable to further interpret negative FC values in terms of which ROI is providing the inhibition and which ROI is receiving inhibition. However, vast evidence from NHP and human studies supports the PFC inhibition of the AMY as pivotal to resilience against anxiety and addiction disorders (Quirk and Gehlert 2006), suggesting that positive AMY-PFC FC during adulthood may be a biomarker for emotional reactivity. Future studies should assess for an association between AMY-PFC FC and adult anxiety levels. Regarding the directionality of the HIPP-AMY FC, previous literature notes that the HIPP sends inhibitory projections to the PFC (Marek et al., 2018; Peters et al., 2010), which reduces the neural activity in the PFC such that it is reduced in its ability to suppress fear expression and to promote fear extinction. Thus, a strong positive HIPP-PFC FC may be an indicator for elevated anxiety and poor emotional regulation. However, most literature documents that the HIPP-PFC FC is altered in individuals with various

psychopathologies compared to controls, but the directionality of the HIPP-PFC FC alterations is dependent upon the type of psychopathology (depression, anxiety disorder, schizophrenia, bipolar disorder) and subject to high individual variability (Kemmotsu et al., 2013; Liu et al., 2020; Cheng et al., 2018; Walther et al., 2022; Han et al., 2019). Therefore, instead of examining the FC between the HIPP-PFC, studies have resorted to assessing the FC variability between the HIPP-PFC; for instance, Zhang et al., 2021 stresses the positive association between trait anxiety and variations in HIPP-PFC FC, suggesting a link between shifted HIPP-PFC FC and deficits in regulating negative and anxious thoughts, but the direction of the HIPP-PFC FC is not reported. As with the HIPP-PFC FC, AMY-HIPP FC also plays a critical role in mediating the expression and preservation of contextual, but hippocampal projections to the AMY seem to stimulate the AMY in order to intensify fear expression (Orsini et al., 2011; Marek et al., 2018; Herry et al., 2008). Although AMY-HIPP FC variability is dependent upon the pathology type and the state of the patient during the fMRI scan, positive AMY-HIPP FCs, which seemingly enhance the fear response, in general may be indicative of psychopathology, such as generalized anxiety disorder, post-traumatic stress disorder (PTSD), paranoia, stemming from elevated anxiety (Walther et al., 2022; Yang et al., 2017; St Jacques et al., 2011; Hakamata et al., 2017). In St Jacques et al., 2011, compared to controls, individuals with PTSD demonstrated greater positive AMY-HIPP FC when participants were asked to retrieve intense negative autobiographical memories, suggesting the role of AMY-HIPP FC in triggering and upkeeping the aversive fear response. Contrastingly, other literature in patients with depression and post-traumatic stress disorder reports reduced positive AMY-HIPP FC in patients with mental illness relative to controls, suggesting the role of strong positive AMY-HIPP FC in protecting against mental health conditions (Sripada et al., 2012; Cullen et al., 2014; Cheng et al., 2018). Cullen et al., 2014 reports reduced positive AMY-HIPP FC in adolescents with major depressive disorder compared to controls, suggesting that strong positive AMY-HIPP FC may provide resilience against symptoms of depression. The neurobiological mechanisms as to why enhanced positive AMY-HIPP FC is associated

with lower stress and decreased depressive symptoms is yet to be uncovered and is an avenue for future research.

Significance:

Despite its limitations, this study is significant as it demonstrates the impact of early life stress (infant maltreatment towards the infant by the mother) on the adult functional connectivity of fronto-limbic neurocircuitry, comprising the amygdala, hippocampus, and the various subregions of the prefrontal cortex. Because it is difficult to isolate the effects of infant maltreatment on brain development and behavior, a major strength of this study was its use of the cross-fostering procedure and the random assignment to a group (MALT, Control) at birth in order to control for the effects of heritable and prenatal factors on postnatal experience. Adding onto the longitudinal investigation examining the effects of maternal abuse and neglect on brain development of the offspring during infancy through adolescence, this study found long-term impact of infant maltreatment on specific corticolimbic neurocircuitry (dorsolateral/ventrolateral prefrontal cortex to hippocampus) regulating cognitive control, but not on prefrontal-amygdala connectivity, that plays a critical role in emotional regulation. The data presented in this study suggest that by adulthood, the brain might have already recovered from some, but not all, of the harmful effects of this early life adverse experience, which has major implications for people who suffer with anxiety and mood disorders as well as deficits in emotional regulation. Additional factors that need to be taken into consideration when examining the adult FC differences between MALT vs control individuals include the potential of revictimization later in life and of elevated levels of gonadal hormones during puberty to alter cortico-limbic circuits in the brain.

TABLES:

Table 1: Group and Sex breakdown based on biological mother group and randomized crossfostering assignment at birth to a Control or MALT foster mother.

	FOSTER mother group							
	Control				MALT			
	males		females		males		females	
Cross from biological to foster mother:	Control to Control	MALT to Control	Control to Control	MALT to Control	Control to MALT	MALT to MALT	Control to MALT	MALT to MALT
	4	0	3	1	4	3	1	5
	n=4		n=4		n=7		n=6	
	n=9 (8 crossfostered+ 1 non-crossfostered Control male)				**n=13**			

Control to Control indicates infants born to a Control biological mother, fostered to a Control mother; Control to MALT indicates infants born to a Control biological mother, but fostered to a MALT mother; MALT to Control indicates infants born to a MALT biological mother, but fostered to a Control mother; MALT to MALT indicates infants born to MALT biological mothers, fostered to a MALT mother.

Table 2: Summary of Functional Connectivity (FC) Findings

ROI-ROI FC	Overall Group Effect	Overall Sex Effect	Group*Sex Effect	Group * Sex* Laterality Effect
Left AMY-right AMY	Control=MALT	Males> Females	N/A	N/A
AMY-Area 14	Control=MALT	Males=Females	N/A	N/A
AMY-Area 24	Control=MALT	Males=Females	N/A	N/A
AMY-Area 25	Control=MALT	Males=Females	N/A	N/A
AMY-Area 32	Control=MALT	Males=Females	N/A	N/A
AMY-Area 11	Control=MALT	Males=Females	N/A	N/A
AMY-Area 13	Control=MALT	Males=Females	N/A	N/A
AMY-Area 9	Control=MALT	Males=Females	N/A	N/A
AMY-Area 45	Control=MALT	Males=Females	N/A	N/A
AMY-Area 46	Control=MALT	Males=Females	N/A	N/A
AMY-Area 47	Control=MALT	Males=Females	N/A	N/A
HIPP-AMY	Control=MALT	Males=Females	N/A	N/A
HIPP-Area 14	Control=MALT	Males=Females	N/A	N/A
HIPP-Area 24	Control=MALT	Males> Females	N/A	N/A
HIPP-Area 25	Control=MALT	Males> Females	N/A	N/A
HIPP-Area 32	Control=MALT	Males=Females	N/A	N/A
HIPP-Area 11	Control=MALT	Males=Females	N/A	N/A
HIPP-Area 13	Control=MALT	Males> Females	N/A	N/A
HIPP-Area 9	Control=MALT	Males=Females	Control Females < MALT Females Control Males > MALT Males	N/A
HIPP-Area 45	Control=MALT	Males=Females	N/A	Left: Control Females < MALT Females in Right: Control Females> MALT Females Left & Right: Control Males> MALT Males
HIPP-Area 46	Control=MALT	Males> Females	N/A	N/A
HIPP-Area 47	Control=MALT	Males=Females	N/A	N/A

Comparison of Functional Connectivity Findings Across Group and Sex: The equals sign (=) indicates that there is no significant difference in FC between the two groups. The greater sign indicates the more positive functional connectivity.

FIGURES

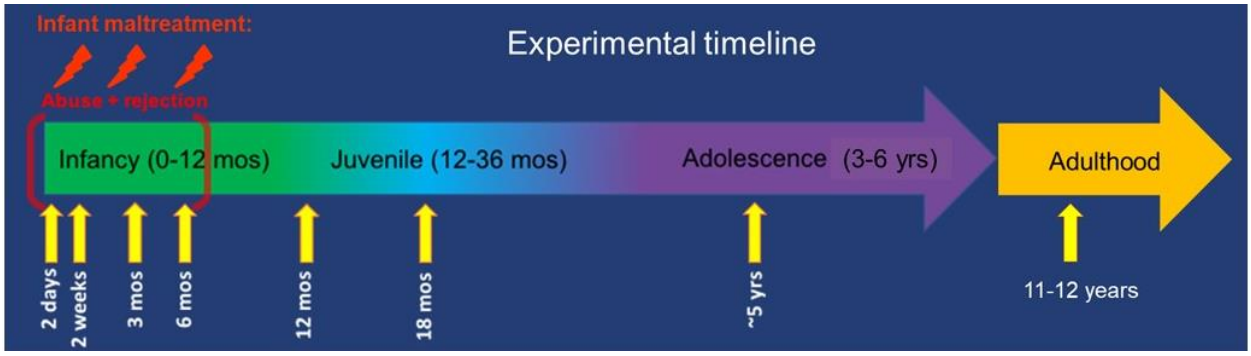

Figure 1: Experimental Timeline. We analyzed the long-term impact of infant maltreatment (MALT)- which consists of abuse and rejection by the mother towards the infant within the first 6 months of life- on the development of functional connectivity (FC) between prefrontal cortex, amygdala and hippocampus during adulthood (11-12 years).

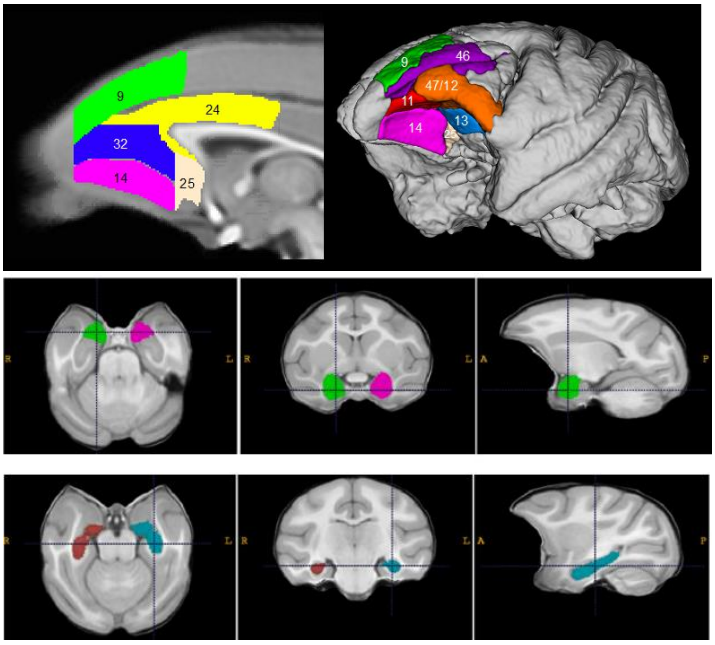

Figure 2: Anatomical location of Regions of Interest (ROIs). (Top) Prefrontal Cortex (PFC) subregions. Resting state fMRI functional connectivity (FC) data were analyzed between the following PFC ROIs and amygdala and hippocampus: medial PFC -mPFC-Areas 14, 24, 25, and 32; orbitofrontal cortex -OFC-areas 11 and 13; dorsolateral PFC -dlPFC- Areas 9 and 46; ventrolateral PFC -vlPFC- Area 47. Not shown in the picture is the frontal eye field (Area 45) located in the vlPFC. (Left) Sagittal view of area 9 and the mPFC regions of interest in the rhesus brain MRI image. (Right) External view of the location of area 14, dlPFC, vlPFC, and OFC regions of interest in 3D rhesus brain MRI image. Images courtesy of Dr. Zsofia Kovacs-Balint. **(Bottom) Views of Amygdala** -top: pink, green- **and Hippocampus** -bottom: blue, red-; From left to right: axial, coronal, and sagittal views [images reproduced from Godfrey et al., 2023].

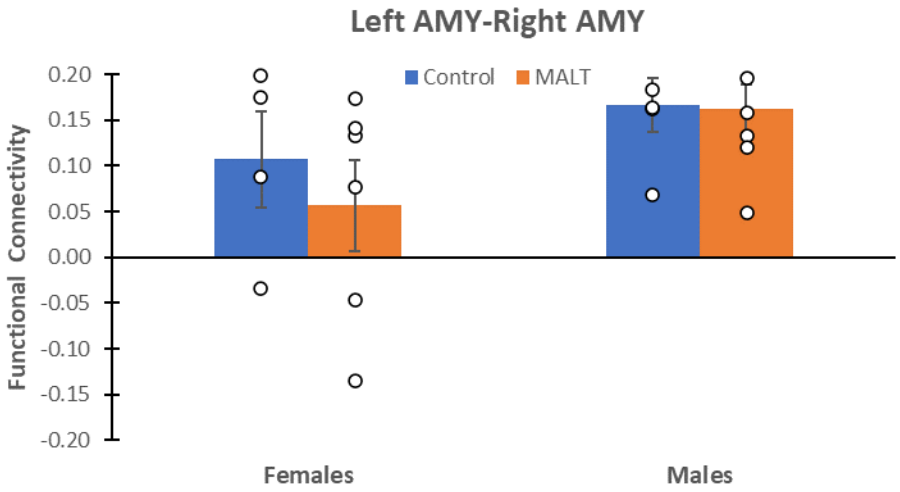

Figure 3: Left amygdala (AMY)-Right AMY functional connectivity (FC). Two-Way ANOVA found no significant main or interaction effects of Group or Sex, although there was a trend towards significance for main Sex effects ($F(1,22) = 4.121$, $p = 0.057$, $\eta p2 = 0.186$); visual inspection of the graphs suggests stronger FC in males than females. Adding Cocaine Intake as a covariate to the statistical model made the Sex effects statistically significant ($F(1,22) = 5.053$, $p = 0.038$, $\eta p2 = 0.229$). Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

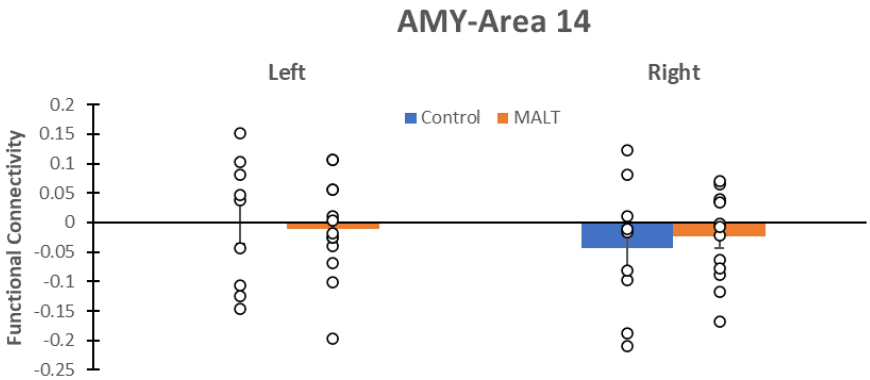

Figure 4: Whole amygdala (AMY)- Area 14 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; RM: Laterality) found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. Visual inspection of data suggests that although the average FC between AMY and Area 14 is close to zero, it is driven by a split distribution of subjects with positive and negative FC within each group. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles

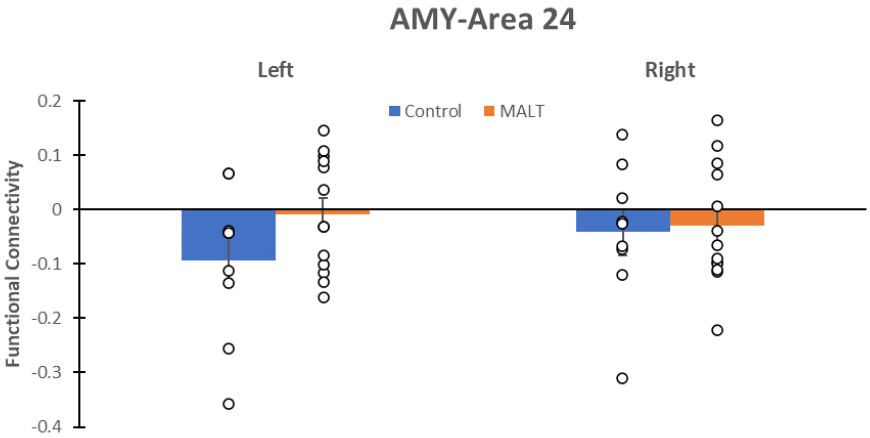

Figure 5: Whole amygdala (AMY)- Area 24 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; RM: Laterality) found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. Visual inspection of the data indicates a split distribution of subjects with positive and negative FC within each group. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

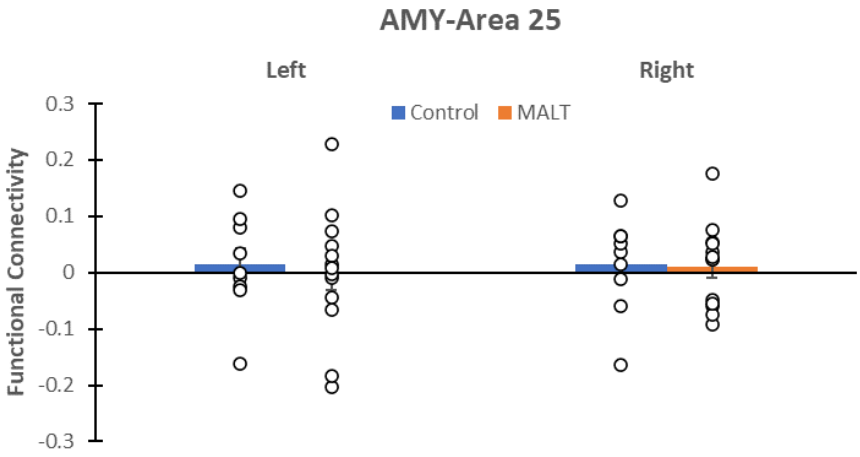

Figure 6: Whole amygdala (AMY)-Area 25 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; RM: Laterality) found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. The data show a split distribution of subjects with positive and negative FC within each group, resulting in an average group FC close to zero. Data in bar charts represent Mean±standard error of the mean (SEM), with individual subjects shown as open circles.

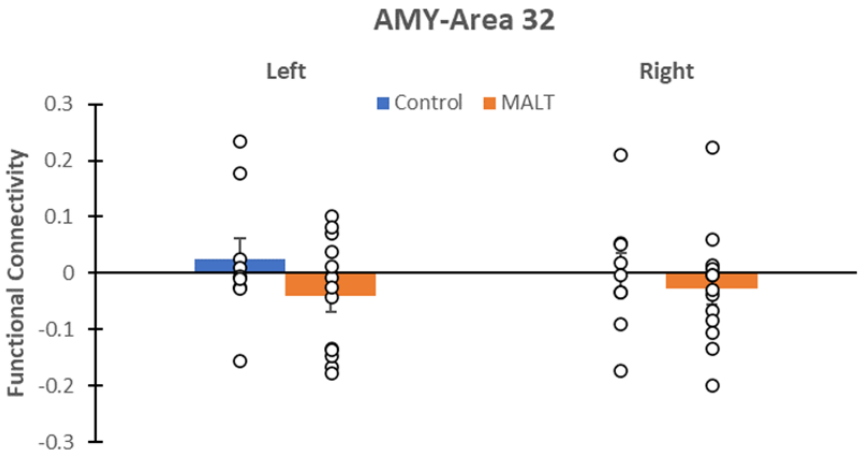

Figure 7: Whole amygdala (AMY)-Area 32 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; RM: Laterality) found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. The data show a split distribution of subjects with positive and negative FC within each group, resulting in an average group FC close to zero. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

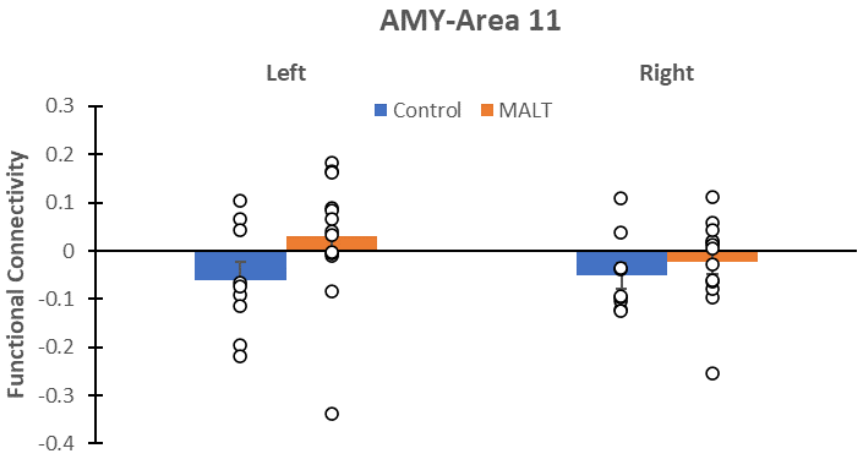

Figure 8: Whole amygdala (AMY)-Area 11 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol and ISO as covariates to the RM ANCOVA showed a main effect of Laterality ($F(1,22) = 4.688$, $p = 0.046$, $\eta p2 = 0.227$) as well as a trend towards significance of an interaction effect of Laterality* ISO ($F(1,22) = 3.977$, $p = 0.063$, $\eta p2 = 0.199$). There is also a split distribution of subjects with positive and negative FC within each group, resulting in an average group FC close to zero. Data in bar charts represent Mean±standard error of the mean (SEM), with individual subjects shown as open circles.

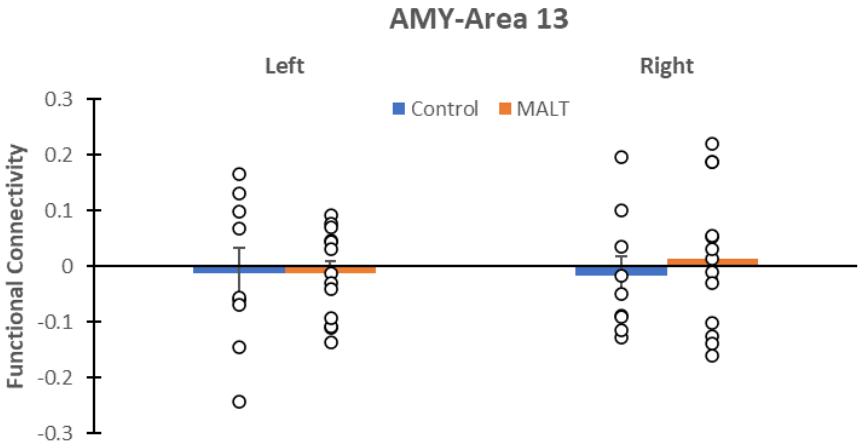

Figure 9: Whole amygdala-Area 13 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol and ISO as covariates to the RM ANCOVA showed a trend towards significance of an interaction effect of Laterality* Telazol ($F(1,22) = 4.305$, $p = 0.055$, $\eta p2 = 0.212$). The graphs show high individual variability with a split distribution of subjects with positive versus negative FC within each group, resulting in an average group FC close to zero. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

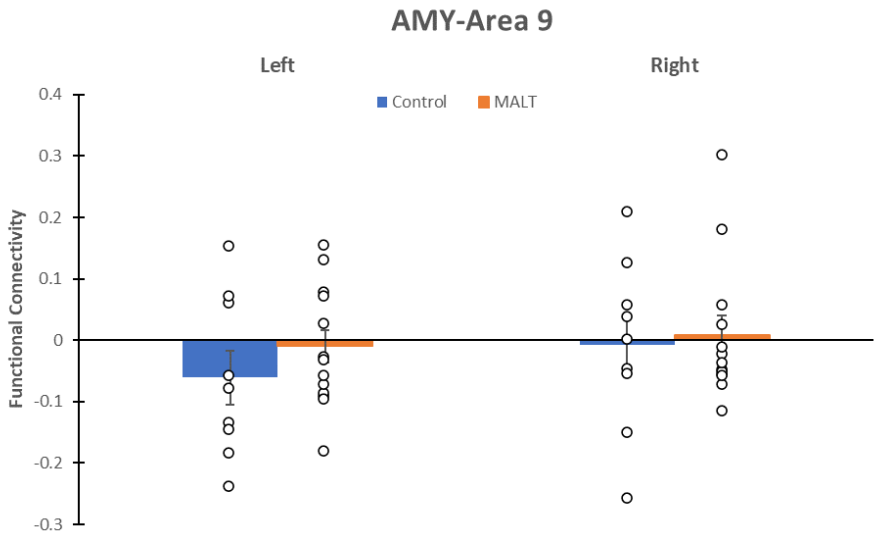

Figure 10: Whole amygdala (AMY)-Area 9 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. The graphs show a split distribution of subjects with positive and negative FC within each group, resulting in an average group FC close to zero. Data in bar charts represent Mean±standard error of the mean (SEM), with individual subjects shown as open circles.

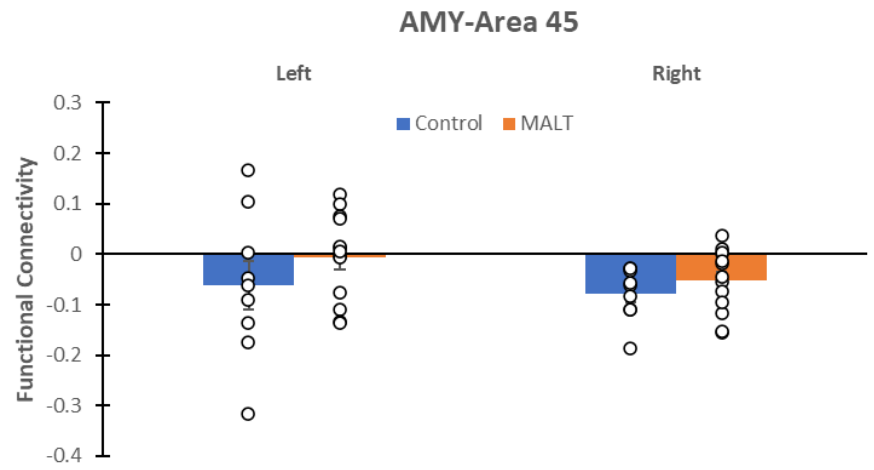

Figure 11: Whole amygdala (AMY)-Area 45 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show any effects of these covariates and did not change the results. The data show a split distribution of subjects with positive and negative FC within each group in the left hemisphere, but mainly a negative FC in the right. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

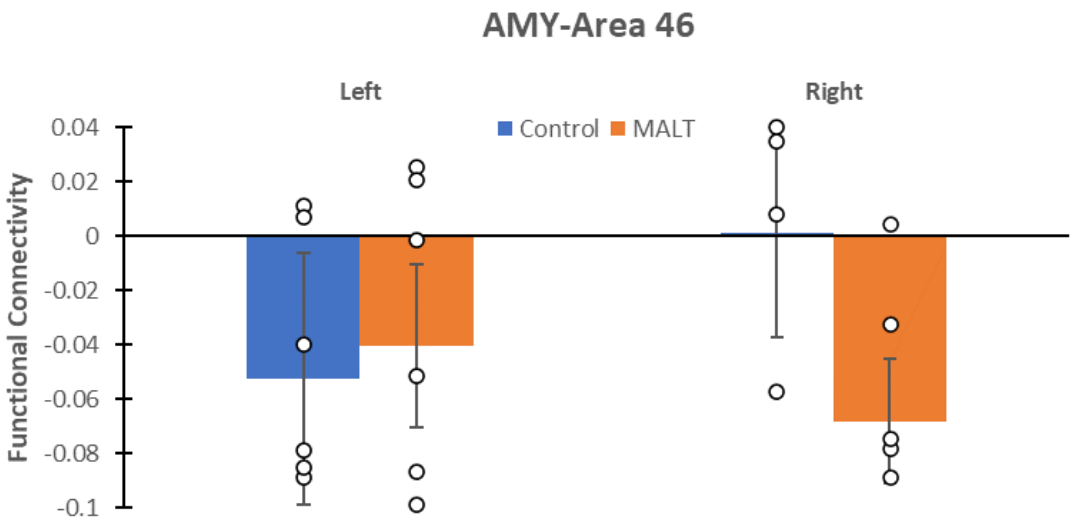

Figure 12: Whole amygdala (AMY)-Area 46 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol, ISO, and Lifetime Cocaine Intake as covariates to the RM ANCOVA did not show effects of these covariates and did not change the results. Although most group FC averages are negative, the data shows individual variability in subjects with positive and negative FC. Data in bar charts represent Mean standard error of the mean(SEM), with individual subjects shown as open circles.

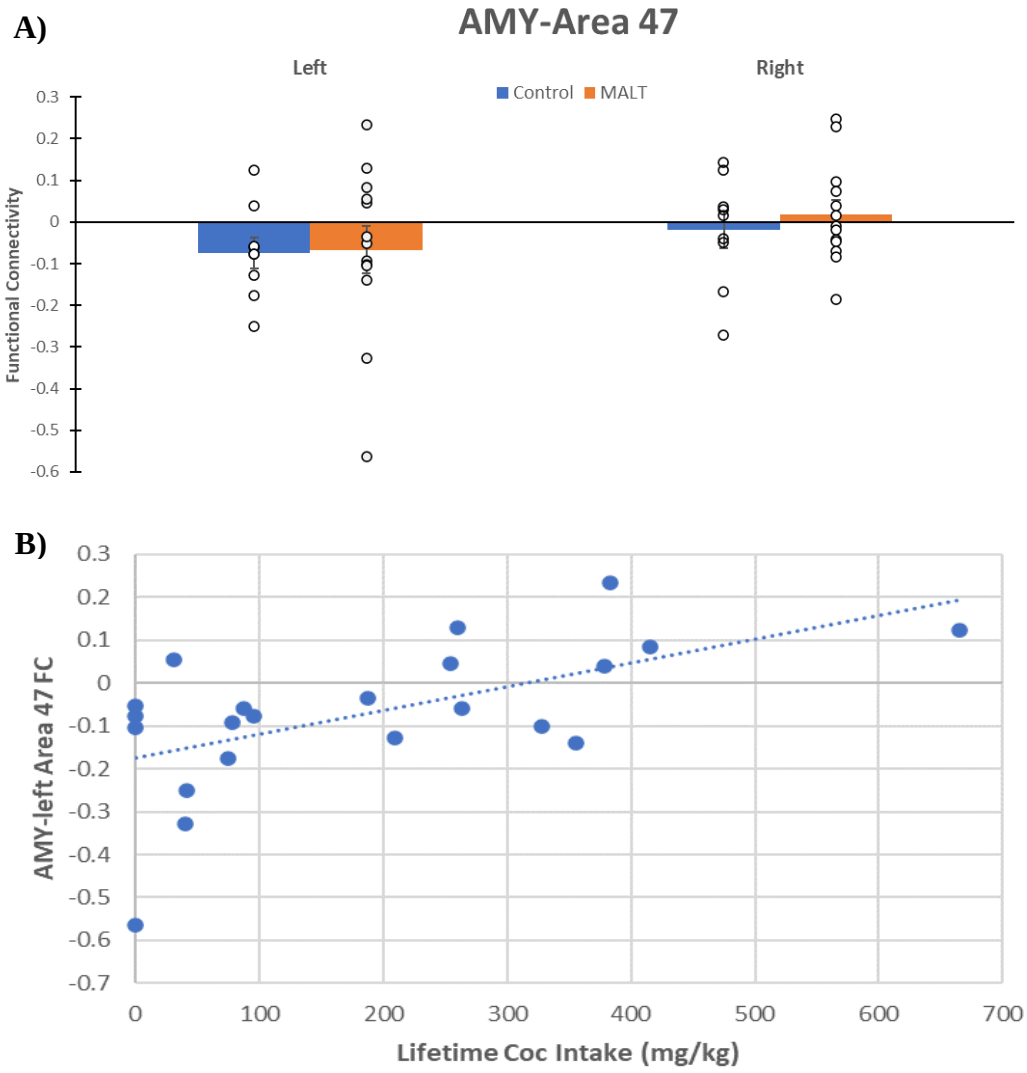

Figure 13A: Whole amygdala (AMY)-Area 47 functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Lifetime Cocaine Intake as a covariate to the RM ANCOVA yielded main effects of Laterality ($F(1,22) = 11.284$, $p = 0.004$, $\eta p2 = 0.399$), Lifetime Cocaine Intake ($F(1,22) = 4.697$, $p = 0.045$, $\eta p2 = 0.216$), and a Laterality * Lifetime Cocaine Intake interaction effect ($F(1,22) = 8.104$, $p = 0.011$, $\eta p2 = 0.323$). The data show a general split of subjects with negative versus positive FC in each group. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subject plots shown as open circles**. Figure 13B: Pearson Correlation between AMY-left Area 47 FC and Lifetime Cocaine Intake**. A strong positive correlation between lifetime cocaine intake and whole AMY-left Area 47 ($r=0.582$; $p=0.004$) was detected, suggesting that the macaques who greater adolescent lifetime cocaine intake experienced a greater positive adult AMY-left Area 47 FC .

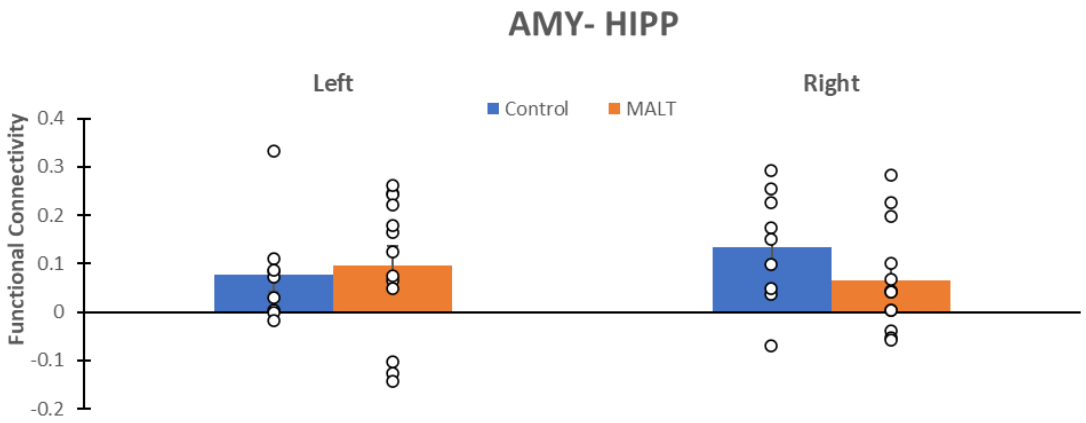

Figure 14: Whole amygdala (AMY)-hippocampus (HIPP) functional connectivity (FC). RM ANOVA found no main or interaction effects of Group, Sex, or Laterality. Adding Telazol and ISO as covariates to the RM ANCOVA showed a trend towards significance of a main effect of Telazol ($F(1,22) = 4.069, p = 0.061, \eta p2 = 0.203$). The data show mainly positive FC in all animals. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

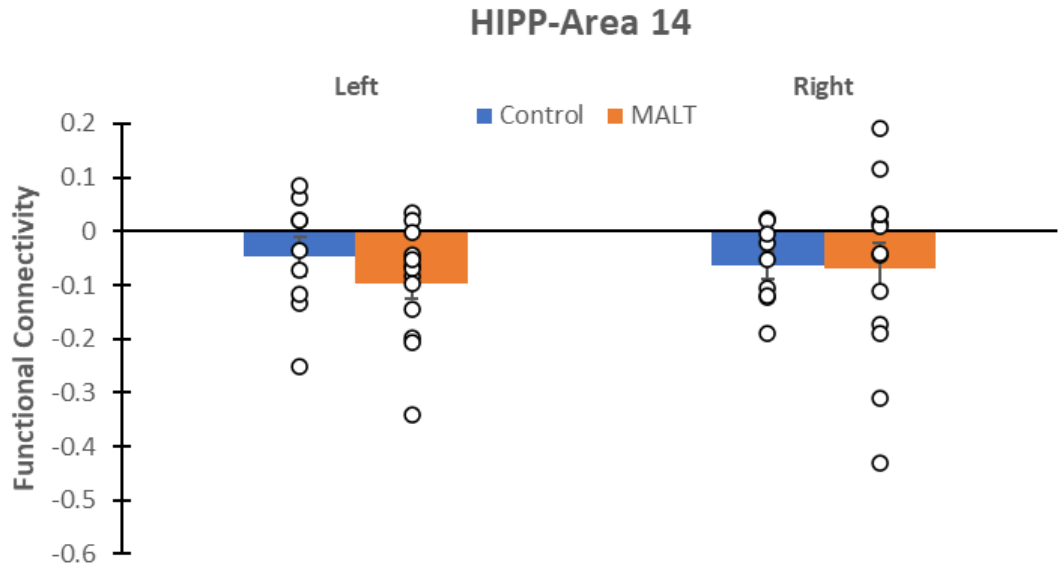

Figure 15: Whole hippocampus (HIPP)-Area 14 functional connectivity (FC). Adding Telazol and ISO as covariates to the RM ANCOVA (fixed factors: Group and Sex; RM: Laterality) yielded, a main effect of ISO ($F(1,22) = 7.156$, $p = 0.017$, $\eta p2 = 0.309$). The data show mainly negative FC in all animals. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

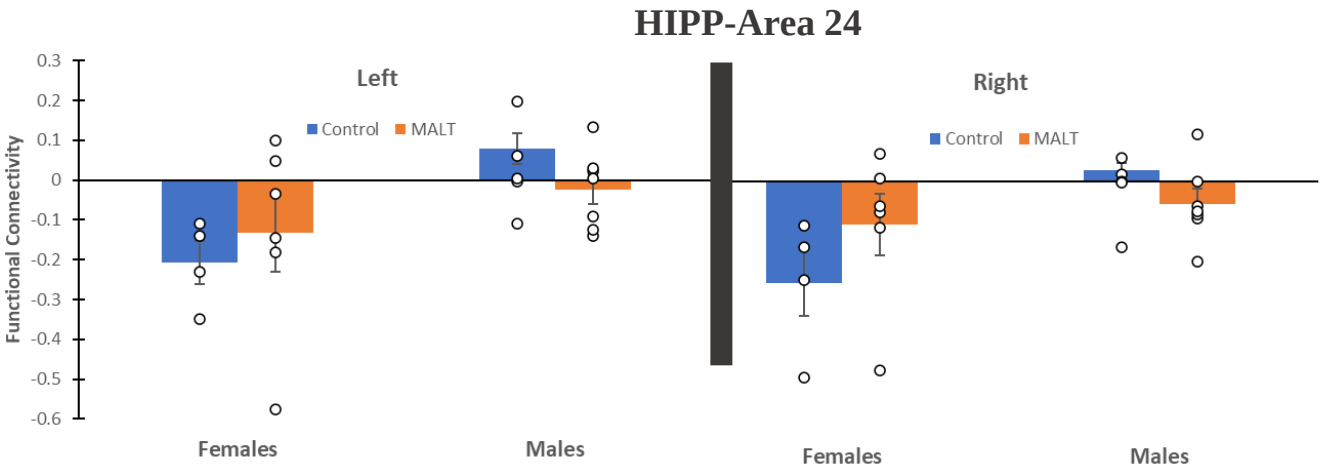

Figure 16: Whole hippocampus (HIPP)- Area 24 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected a main effect of Sex ($F(1,22)=9.692$, $p=0.006$, $\eta p2 = 0.350$). The data shows a strong negative FCs in the females, while the males have weak positive and negative FCs. Adding Telazol and ISO as covariates to the RM ANCOVA maintained the main effect of Sex ($F(1,22) = 6.343$, $p = 0.023$, $\eta p2 = 0.284$), while also yielding main effects of Telazol ($F(1,22) = 5.554$, $p = 0.032$, $\eta p2 = 0.258$) and ISO ($F(1,22) = 5.998$, $p = 0.026$, $\eta p2 = 0.273$). Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

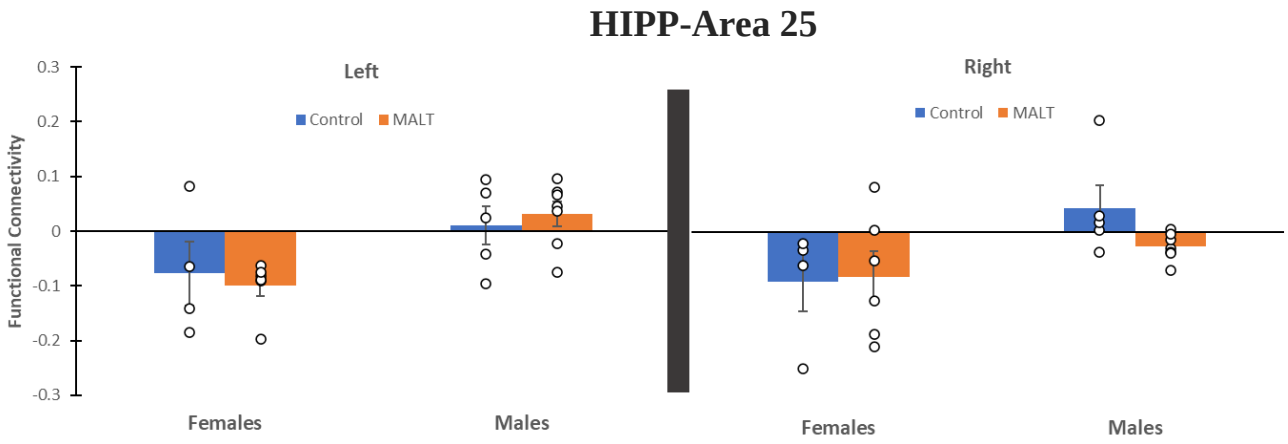

Figure 17: Whole hippocampus (HIPP)-Area 25 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected a main effect of Sex ($F(1,22) = 12.714$, $p = 0.002$, $\eta p2 = 0.414$). The data shows a strong negative FC in the females, while the males have weak positive and negative FCs. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

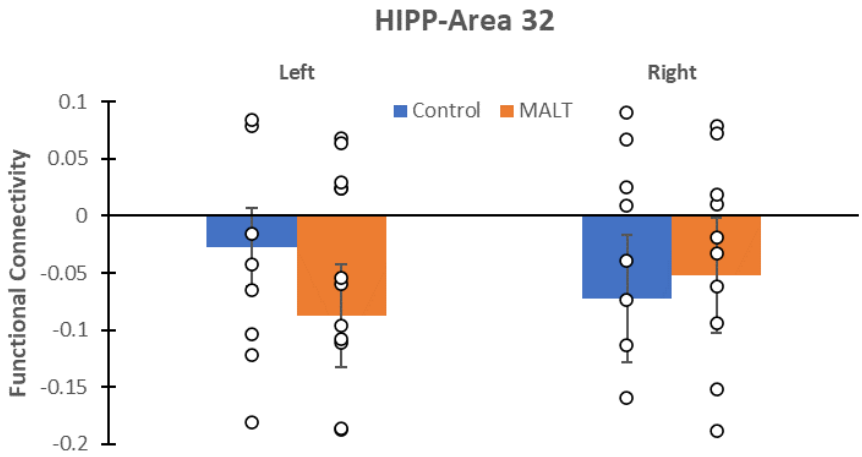

Figure 18: Whole hippocampus (HIPP)-Area 32 functional connectivity (FC). Adding Telazol and ISO as covariates to the RM ANCOVA (fixed factors: Group and Sex; repeated measures: Laterality) yielded main effects of Telazol ($F(1,22) = 9.098$, $p = 0.008$, $\eta p2 = 0.363$) and ISO ($F(1,22) = 6.130$, $p = 0.025$, $\eta p2 = 0.277$). The data indicates a split distribution of subjects with positive and negative FCs within each group. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

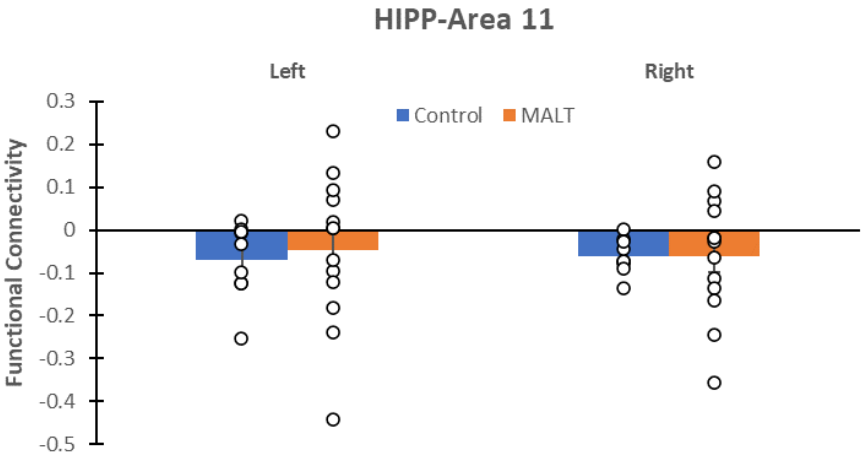

Figure 19: Whole Hippocampus (HIPP)-Area 11 functional connectivity (FC). Adding Telazol and ISO as covariates to the RM ANCOVA (fixed factors: Group and Sex; repeated measures: Laterality) yielded main effects of Telazol ($F(1,22) = 5.452$, $p = 0.033$, $\eta p2 = 0.254$) and of ISO ($F(1,22) = 12.436$, $p = 0.003$, $\eta p2 = 0.437$). The data shows a bias towards a negative FC in the Control animals, and in the MALT animals, a split distribution of subjects with positive and negative FCs is exhibited. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

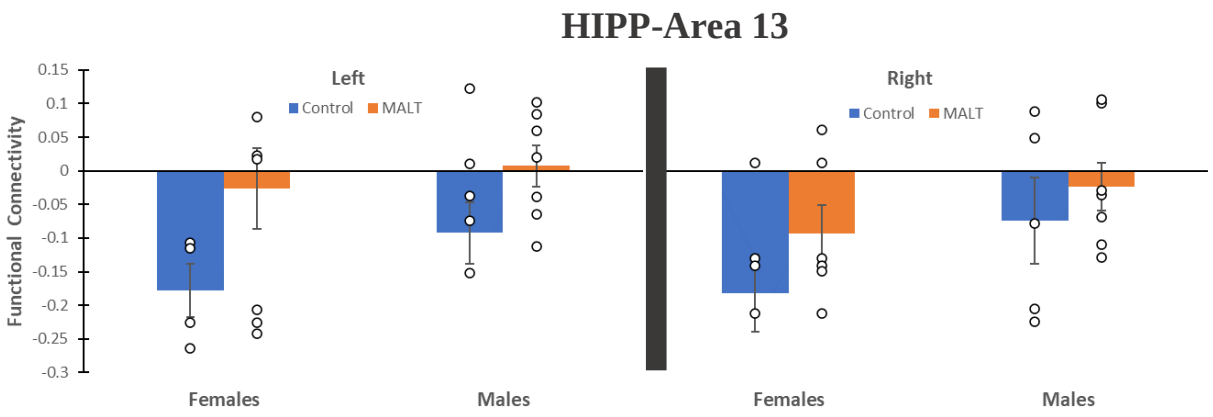

Figure 20: Whole hippocampus (HIPP)- Area 13 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected a main effect of Sex ($F(1,22) = 7.861$, $p = 0.012$, $\eta p2 = 0.304$). The data shows a negative FC in the females, while the males also exhibit a negative FC with the exception of the MALT males in the left hemisphere. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

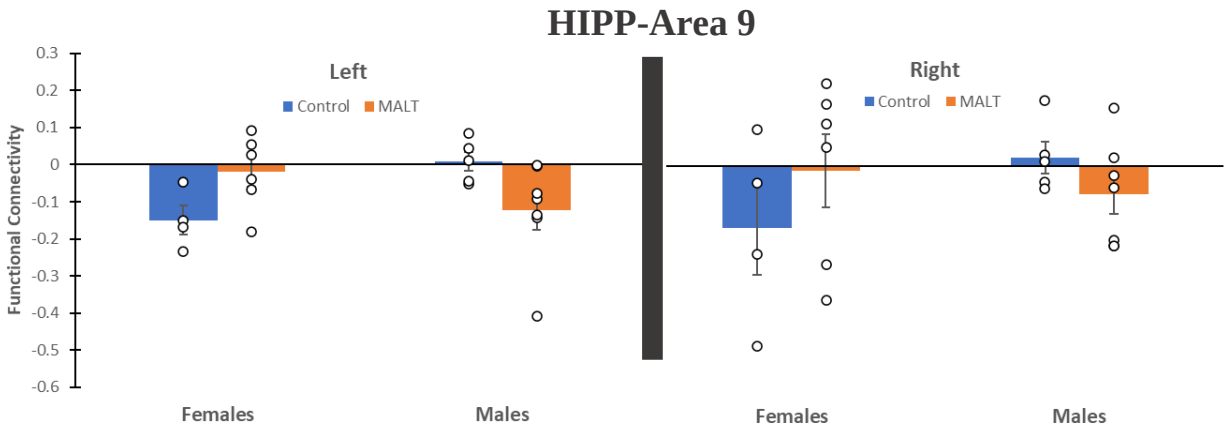

Figure 21: Whole hippocampus (HIPP)-Area 9 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected an interaction effect of Group *Sex ($F(1,22) = 5.365$, $p = 0.033$, $\eta p2 = 0.230$). The data indicates that while Control females exhibited a stronger negative FC than the MALT females, the Control males showed a weaker positive FC compared to MALT males, whom exhibited a strong negative FC. Adding Telazol and ISO as covariates to the RM ANCOVA yielded a main effect of Laterality ($F(1,22) = 6.761$, $p = 0.019$, $\eta p2 = 0.297$) ,an interaction effect of Laterality * Telazol ($F(1,22) = 5.860$, $p = 0.028$, $\eta p2 = 0.286$), and an interaction effect of Laterality * ISO ($F(1,22) = 4.863$, $p = 0.042$, $\eta p2 = 0.233$). Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

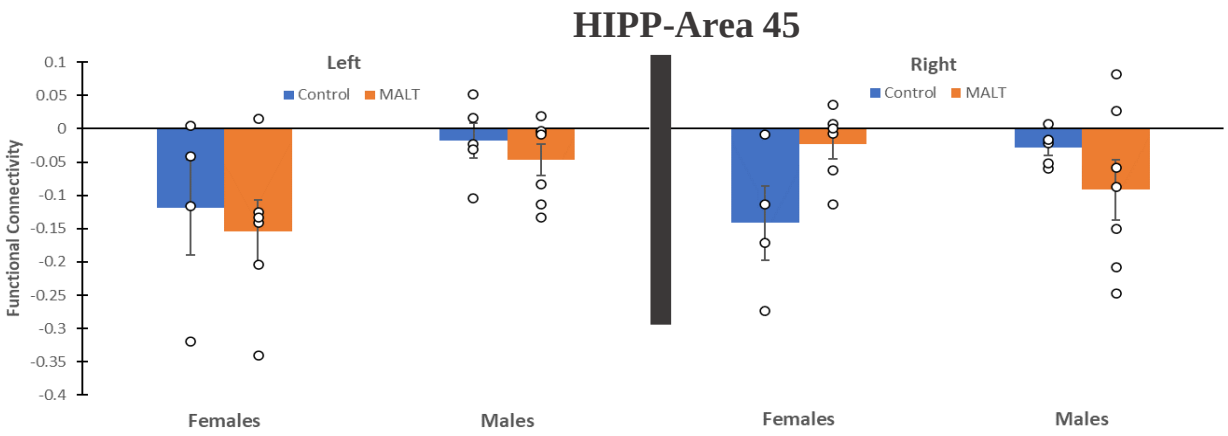

Figure 22: Whole hippocampus (HIPP)-Area 45 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected an interaction effect of Group*Sex*Laterality $F(1,22) = 5.703$, $p = 0.028$, $\eta p2 = 0.241$). Adding Lifetime Cocaine Intake as a covariate to the RM ANCOVA yielded an interaction effect of Laterality * Sex ($F(1,22) = 4.540$, $p = 0.048$, $\eta p2 = 0.211$). The data shows that females display stronger negative FC than the males in most groups. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

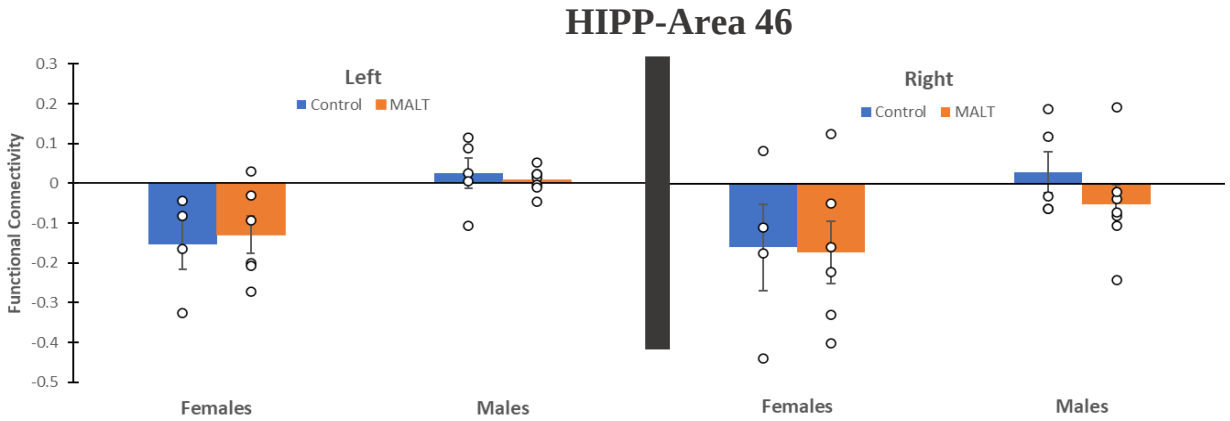

Figure 23: Whole hippocampus (HIPP)-Area 46 functional connectivity (FC). RM ANOVA (fixed factors: Group and Sex; repeated measures: Laterality) detected a main effect of Sex ($F(1,22) = 9.692$, $p = 0.006$, $\eta p2 = 0.350$). The data shows mostly strong negative FC in the females, while the males have weak positive and negative FC. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

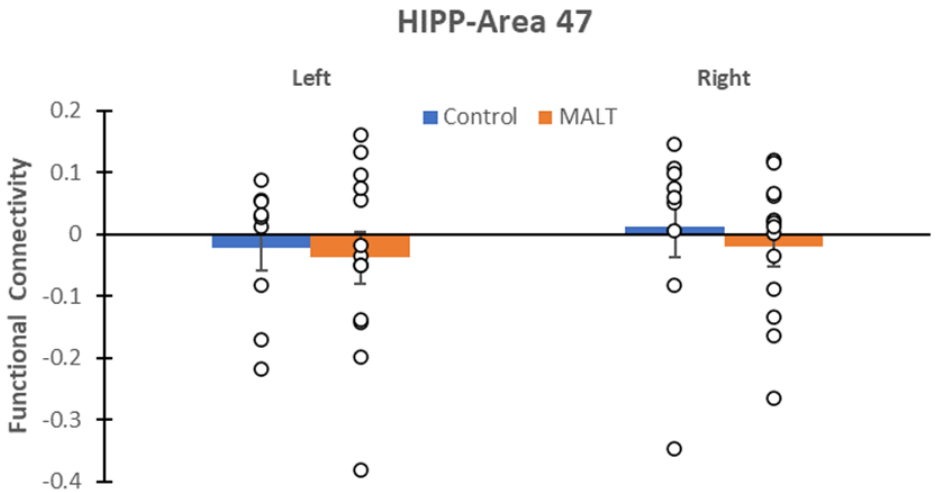

Figure 24: Whole hippocampus (HIPP)-Area 47 functional connectivity. Adding Telazol and ISO as covariates to the RM ANCOVA (fixed factors: Group and Sex; repeated measures: Laterality) showed a trend towards significance of a main effect of Telazol ($F(1,22) = 4.693$, $p = 0.046$, $\eta p2 = 0.227$). The data indicates a split distribution of subjects with positive and negative FCs within each group. Data in bar charts represent Mean±standard error of the mean(SEM), with individual subjects shown as open circles.

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