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# Long-term behavioural and neurocognitive outcomes after exposure to early psychosocial deprivation in rhesus macaques: A longitudinal study

Alice Massera

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**Effets neurocognitifs et comportementaux à long terme après  
l'exposition à une privation psychosociale précoce chez les macaques  
rhésus: Une étude longitudinale**

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**Long-term behavioural and neurocognitive outcomes after exposure to  
early psychosocial deprivation in rhesus macaques: A longitudinal study**

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*'Self Portrait with Monkeys' by Frida Kahlo, 1943*





To Malia, Marlee, Millie, Marcel, Smeagal, Oliver, Neville,  
Adelina, Guendalina, Lothario, Ralph, Freddie, William,  
Mr Spaghetti, Flea, Cruella, Courtney, Joni, Kurt, Lou,  
with a special thought for **Malachi**.

*The soft breeze touches your skin,  
Making you unsure of where to begin.  
A dragon roars within, seeking to break free,  
Wanting control and its voice to be heard, loud and clear.  
That joy you once felt now kneels in defeat,  
Its hold on you, powerless and incomplete.  
In your moment of need, who will come to your aid?  
The arrogant or the self-centered, both unafraid?  
They ignore the wrongs done and show no care,  
Leaving you to face this burden, a heavy cross to bear.  
They cannot understand what you truly seek,  
As you strive to liberate your spirit, strong and free.  
You must slay the dragon inside,  
But in your quest, you are alone,  
with tears you cannot hide.*



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This thesis is a testament to the dedication and hard work of many individuals, and I am deeply grateful for all their contributions. Thank you all for your support and encouragement.

Sincerely,

*Alice*





# RESUME

L'objectif de cette thèse de doctorat était d'étudier les effets à long terme de la privation psychosociale précoce sur l'autorégulation chez les macaques, en mettant l'accent sur les fonctions exécutives et ses corrélats neuraux sous-jacents. Les principaux résultats suggèrent que la privation psychosociale précoce est associée à des déficiences des fonctions exécutives des macaques à l'adolescence, et que ces déficiences persistent au début de l'âge adulte. La fonction exécutive était liée au développement structurel du cortex préfrontal et à sa connectivité avec les structures cérébrales pariétales et striatales. Le développement atypique du cortex préfrontal et de sa connectivité était lié à des aspects spécifiques des fonctions exécutives appauvries chez les macaques exposés à une privation précoce, avec un certain soutien fourni pour un mécanisme compensatoire favorisant certains aspects des fonctions exécutives au détriment du développement ultérieur et des résultats connexes. D'autres résultats démontrent également un traitement anormal de la menace, une dérégulation des émotions et un risque accru d'anxiété après une privation psychosociale précoce chez les macaques. Les résultats ont été interprétés à la lumière des théories actuelles sur les trajectoires de développement après une exposition à l'adversité sociale précoce. Les modèles de stress et de plasticité sont examinés, y compris les modèles dimensionnels qui mettent en évidence la menace par rapport à la privation comme des éléments clés conduisant à des résultats différents après une privation psychosociale précoce. Des modèles plus récents suggèrent que l'imprévisibilité de l'environnement et d'autres aspects de l'adversité, au-delà de la menace et de la privation, jouent un rôle important, et que de nombreuses formes d'adversité sociale précoce impliquent un mélange de menace, de privation et/ou d'imprévisibilité, ainsi que des mécanismes distincts et superposés liant l'adversité précoce à un développement neurocognitif atypique. Les résultats de cette thèse soutiennent cette dernière théorie. Les points forts et les limites de la recherche actuelle sont également explorés. Parmi les points forts, citons la conception de la recherche longitudinale qui inclut un point de temps adolescent (c'est-à-dire une période centrale de risque de mauvais résultats liés à la privation psychosociale précoce, tels que les troubles de l'humeur et les problèmes d'extériorisation) ; l'utilisation de mesures objectives pour évaluer le comportement ; le suivi simultané du développement cérébral et comportemental dans le temps ; l'utilisation d'une approche multidisciplinaire impliquant des domaines tels que

l'éthologie, les neurosciences et la psychologie ; et l'utilisation de techniques multimodales, notamment l'imagerie par résonance magnétique, l'observation comportementale et la modélisation informatique. Toutefois, les limites de la recherche, telles que la petite taille de l'échantillon, l'absence de points d'évaluation antérieurs ou postérieurs et l'absence d'examen du mécanisme d'apprentissage spécifique (par exemple, associatif ou de renforcement) lié au développement atypique, ont également été reconnues. Plusieurs orientations en termes d'étapes futures dans le cadre du projet présenté ici et ce domaine de recherche en général sont proposées dans le dernier chapitre. Dans le cadre du projet actuel, l'analyse de mesures cérébrales supplémentaires, y compris la myélinisation et l'IRM de l'état de repos, l'étude du système dopaminergique et l'exploration de la manière dont les aspects cognitifs et émotionnels de l'autorégulation interagissent pour prédire des résultats tels que l'anxiété ou les symptômes de type TDAH seront réalisés. Dans les recherches futures, il sera important de mener des études longitudinales sur un plus grand nombre de stades de développement, d'étudier les mécanismes d'apprentissage spécifiques affectés par la privation psychosociale précoce et de comparer les effets de différents types d'adversité précoce. En conclusion, les principaux résultats présentés dans cette thèse fournissent des informations nouvelles et précieuses sur les effets à long terme de la privation psychosociale précoce sur les fonctions exécutives et ses mécanismes neuronaux sous-jacents chez les macaques. Des recherches supplémentaires sont maintenant nécessaires pour mieux comprendre les différentes trajectoires de développement suite à une adversité sociale précoce, en comparant avec des résultats sains ou pathologiques. Cela sera essentiel pour la conception de futurs traitements et d'interventions visant à améliorer et à prévenir les mauvais résultats dans le contexte de l'adversité sociale précoce, et donc à améliorer la qualité de vie des personnes concernées.

**Mots-clés :** Privation psychosociale précoce, macaques rhésus, autorégulation, fonction exécutive, imagerie par résonance magnétique, longitudinal

# ABSTRACT

The aim of this thesis was to investigate the long-term effects of early psychosocial deprivation on self-regulation in macaque monkeys, with a particular focus on executive function and its underlying neural correlates. The main results suggest that early psychosocial deprivation is associated with impairments in macaque executive function during adolescence, and that such impairments persist into early adulthood. Executive function was related to structural development of the prefrontal cortex and its connectivity with parietal and striatal brain structures. Atypical development of prefrontal cortex and its connectivity was related to specific aspects of poor executive function in macaques exposed to early deprivation, with support provided for a compensatory neural mechanism promoting some aspects of executive function in these animals, but at the expense of subsequent brain development and related poor outcomes. Additional findings also demonstrate abnormal threat processing, emotion dysregulation, and increased risk for anxiety in the context of early psychosocial deprivation in macaques. The results were interpreted in light of current theories on different developmental trajectories after exposure to early social adversity. Theories of stress and plasticity are discussed, as well as conceptual models highlighting how different aspects of early adverse environments may lead to different outcomes after early social adversity, such as threat versus deprivation. More recent models proposing that environmental unpredictability and other aspects of adversity beyond threat and deprivation play an important role are also discussed, as well as the idea that many forms of early social adversity likely involve a mix of threat, deprivation, and/or unpredictability, as well as both distinct and overlapping mechanisms linking early adversity to atypical neurocognitive development. Findings from this thesis support this latter proposal. Strengths and limitations of the current research are also explored. Key strengths include the longitudinal research design, which includes an adolescent time-point (i.e. a core period of risk for negative outcomes linked to early psychosocial deprivation such as mood disorders and externalizing problems); use of objective measures to assess behaviour; simultaneous tracking of brain and behavioural development across time; the use of a multidisciplinary approach spanning areas such as ethology, neuroscience, and psychology; and the use of multimodal techniques including magnetic resonance imaging, behavioural observation, and computational modelling. However, limitations of the research such as small sample size, lack of additional

assessment time-points, and the inability to examine specific learning mechanisms (e.g. associative or reinforcement) via which early adversity may relate to atypical development are also acknowledged. Several directions concerning future steps for the wider project, and the research field in general, are proposed in the final chapter. In terms of the current project, analysis of additional brain measures, including myelination and resting-state MRI, investigation into the dopaminergic system, and exploration of how cognitive and emotional aspects of self-regulation interact to predict outcomes such as anxiety or ADHD-like symptoms in macaques exposed to early psychosocial deprivation will now be conducted. In terms of the research field in general, it will be important in the future to conduct longitudinal studies across more stages of development, to investigate specific learning mechanisms impacted by early psychosocial deprivation, and to compare the effects of different types of early adversity on specific outcomes. In conclusion, the principal findings presented in this thesis provide novel and valuable insights into the long-term effects of early psychosocial deprivation on executive function and underlying neural mechanisms in macaque monkeys. Further research is now needed to more fully understand how different trajectories of development emerge after early social adversity, and how these are associated with healthy versus pathological outcomes. This will be essential for the design and implementation of treatments and interventions to ameliorate and prevent poor outcomes in the context of early social adversity, and thus improve the quality of life for affected individuals.

**Key words:** Early psychosocial deprivation, rhesus macaques, self-regulation, executive function, magnetic resonance imaging, longitudinal

# PREFACE

In this Ph.D. thesis, I present my work on the longitudinal effects of early psychosocial deprivation on neurocognitive and behavioural development in rhesus macaques (*Macaca mulatta*). I completed this research at the Institut des Sciences Cognitives – Marc Jeannerod (ISC-MJ) CNRS, in the Laboratory of Social Neuroscience and Comparative Development led by Pier Francesco Ferrari. Dr Ferrari served as my main supervisor, with Dr Holly Rayson, a postdoctoral researcher in my team, and Dr James Bonaiuto, who heads the Decision, Action, and Neural Computation lab at the ISC-MJ, also giving additional supervision. All the magnetic resonance imaging (MRI) work presented in my thesis was conducted in collaboration with Drs Bassem Hiba and Suliann Ben Hamed, who are also based at the ISC-MJ, and their research teams.

In **Chapter I**, a literature review is given. This includes information on the historical bases of research on the effects of early social experience on development, on current theories of how early psychosocial adversity may lead to long-term poor outcomes in many developmental domains, and details about current evidence in support of these theories and outstanding questions. In **Chapter II**, methods utilized in the wider project of which the research presented in this thesis is part is described, including information about the project design, the subjects, and all assessments conducted. In **Chapter III**, longitudinal effects of early psychosocial deprivation on macaque executive function are explored, both in adolescence and early adulthood, and in **Chapter IV**, aspects of structural brain development via which poor executive function may arise are investigated. In **Chapter V**, the main findings presented in the previous chapters are discussed, as well as future steps for the project and for the research field in general. In **Appendices A, B, and C**, additional work related to the wider longitudinal project is presented, including results concerning emotion regulation and anxiety, brain development across all three assessment time-points, and posters based on work from this project that were presented at various conferences.

# PUBLICATIONS AND PRESENTATIONS

*\*joint first author, \*\* joint last author*

## Papers

Rayson, H., **Massera, A.**, Belluardo, M., Ben Hamed, S., & Ferrari, P. F. (2021). Early social adversity modulates the relation between attention biases and socioemotional behaviour in juvenile macaques. *Scientific reports*, *11*(1), 1-11.

**Massera, A.**, Bonaiuto, J.J., Gautier-Martins, M., Costa S., Rayson, H.\*\*, & Ferrari, P.F.\*\* (*in press*). Longitudinal effects of early psychosocial deprivation on macaque executive function: Evidence from computational modelling. *Proceedings of the Royal Society B: Biological Sciences*.

Goupil, N., Hochmann, J.R., Rayson, H., **Massera, A.**, Ferrari P.F., & Papeo, L. (*under review*). Genesis of a visual bias toward third-party social interactions. *Current Biology*.

**Massera A.\***, Errame H.\*, Bonaiuto J., Froesel M., Bihan-Poudec Y., Gacoin M., Belluardo M., Richard N., Ben Hamed S., Hiba B., Rayson H.\*\*, & Ferrari P.F\*\*. (*in prep.*). Neural bases of poor executive function in macaques exposed to early psychosocial deprivation: A longitudinal DTI study.

## Selected posters and talks

**Massera A.\***, Errame H.\*, Bonaiuto J., Froesel M., Bihan-Poudec Y., Gacoin M., Belluardo M., Richard N., Ben Hamed S., Hiba B., Rayson H.\*\*, & Ferrari P.F.\*\* (2023). Neural bases of poor executive function in macaques exposed to early social adversity: A longitudinal DTI study. *Poster to be presented at Society for Research in Child Development*.

**Massera, A.**, Rayson, H., Bonaiuto, J., Belluardo, M., Ben Hamed, S., & Ferrari, P.F. (2021). Early social adversity influences executive function in juvenile macaques. *Poster and short talk presented at NeuroFrance*.

**Massera, A.,** Rayson, H., Bonaiuto, J., Belluardo, M., Ben Hamed, S., & Ferrari, P.F (2021). Early social adversity influences executive function in juvenile macaques. *Short talk at the Budapest CEU Conference on Cognitive Development.*

**Massera, A.,** Rayson, H., Belluardo, M., Gacoin, M., Froesel, M., Ben Hamed, S., & Ferrari, P.F (2019). The role of early social experience in the development of ADHD in rhesus macaques. *Poster presented at the Institut des Sciences Cognitives Marc Jeannerod PhD Workshop.*



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# **CHAPTER 1.**

## **Introduction**



## Brain plasticity and critical periods

Early life experience plays a crucial role in shaping the neural pathways that underlie cognitive, emotional, and perceptual abilities, with the early foundations of brain architecture laid down via ongoing interactions between genetic and environmental factors. In the 1940s, Donald Hebb posited that the cellular basis of learning and memory arises from increased synaptic efficacy through the repeated and persistent stimulation of a postsynaptic cell by a presynaptic cell (Hebb, 1949). This theory was later extended to any situation involving a long-lasting modification of synaptic connectivity, including brain circuit development (Brown, 2020; Lazari et al., 2022). According to this theory, reinforced synapses, strengthened by developmental activity, will be retained and tend to expand their connections, while unused ones will be eliminated. As a result, the formation and growth of synapses and neurons will be influenced by postnatal experience. From birth through adolescence, such neural changes coincide with the acquisition of sensory and motor skills, social interaction capacities, and increasingly sophisticated cognitive abilities (Fisher et al., 2017; Johansen et al., 2014; Keyzers & Perrett, 2004; Martin & Morris, 2002; McDonald et al., 2020; Ryan et al., 2015). Therefore, a relationship between behaviour and postnatal, experience-dependent synaptic changes plays a key role in shaping the brain's anatomic-functional architecture and ability to navigate the complex and dynamic environment in which we live.

'Critical periods' are specific periods in which the impact of neural activity and the acquisition and execution of a particular behaviour is maximized. For example, newborns who have a lens deficit (e.g. cataracts) or eye misalignment (strabismus), both of which result in the loss of visual input from one eye to the visual system, can develop a form of functional blindness called amblyopia. Research by Hubel and Wiesel with cats and monkeys showed that this occurs because the cortical neurons related to the impaired eye are unable to establish normal connections with thalamic inputs (Hubel et al., 1977; Wiesel & Hubel, 1965). Crucially, if these eye abnormalities are corrected early in development, vision impairment can be prevented, but if corrected later, vision problems will persist (Hensch, 2004; Huberman et al., 2002). Evidence for critical periods of early brain plasticity also comes from patients who sustained brain damage. If sustained early on in life, such damage is less debilitating than brain damage later on, a generalization known as the Kennard Principle, and based on research with monkeys by Margaret Kennard (Kennard, 1940; Kennard & Kessler, 1940).

The concept of "imprinting" also highlights the importance of critical periods for the emergence of particular behaviours or abilities. Imprinting is a type of rapid learning that occurs early in the life of social animals, which establishes a behavioural pattern such as recognition of and attraction to conspecifics of their own species or a surrogate. This was first described by Douglas Spalding in 1870, and later studied by Konrad Lorenz with ducks. Lorenz found that ducks identify their mother as the first moving thing (including a person) experienced in a visual, auditory, or tactile way immediately after birth (Lorenz, 1935). He also discovered that the time-frame for imprinting in ducks is less than one day; if newborn ducks do not receive an appropriate stimulus within this time frame, they are unable to establish an adequate parental relationship. Subsequent research on other animals, including rats, birds, and sheep, has shown that this type of bonding can also occur in a bidirectional way between mothers and their offspring (Immelmann, 1972; Marr & Lilliston, 2008; Poindron et al., 2007).

## **Early social experience and attachment**

Early findings concerning critical periods of brain development and imprinting influenced the subsequent work of Harry Harlow and his colleagues at the University of Wisconsin in the 1950s on infant attachment (Harlow, 1959). These researchers separated rhesus macaque (*Macaca mulatta*) infants from their biological mothers a few hours after birth, and raised them without any human substitute parent. In one well-known experiment, the infant monkeys were placed in the presence of two different inanimate 'maternal' surrogates: one was a simple wire and wood construction, and the other was covered in foam rubber and soft cloth material. The infants were assigned to one of two conditions. In the first, the wire mother had a milk bottle and the cloth mother did not; in the second, the cloth mother had a milk bottle while the wire mother had none. In both conditions, Harlow found that the infant monkeys spent significantly more time with the cloth mother than they did the wire mother. When only the wire mother had food, the infant came to the wire mother to feed then immediately returned to the cloth surrogate. Harlow also compared socially deprived infants to non-isolated monkeys (Harlow & Zimmermann, 1959). He observed that while the non-isolated monkeys developed into healthy adults, the monkeys reared in isolation with the surrogate mothers all displayed dysfunctional behaviour (e.g. more aggression, more fear, and motor stereotypies). Therefore, Harlow's research was some of the

first to demonstrate that maternal care was emotional, not just physiological, and that early social experiences were essential for healthy behavioural development. These studies provided novel empirical evidence for the centrality of the parent-child relationship and the importance of maternal touch for infant development.



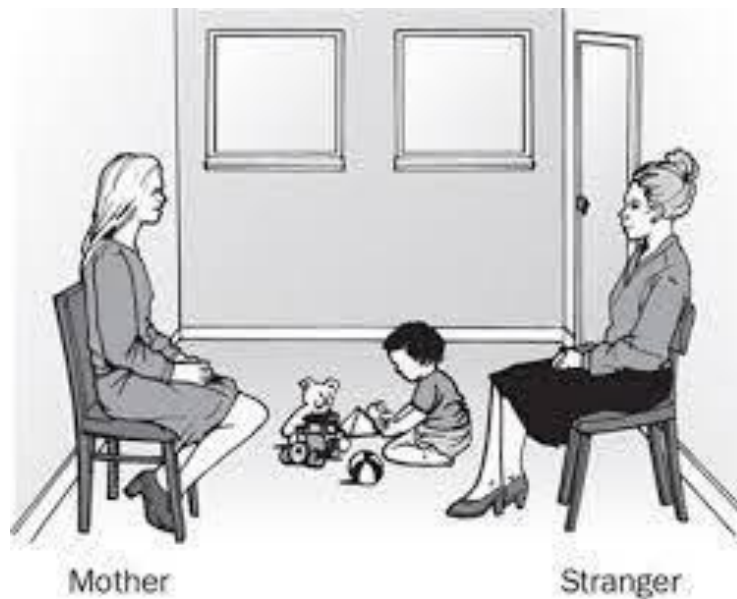
**Figure 1.** *Infant rhesus macaque with cloth and wire mother surrogates* (Figure from Harlow & Zimmermann, 1959).

René Spitz was a psychiatrist who studied infants and children in orphanages and prisons before Western medicine understood or acknowledged the importance of early social connection for healthy development (Spitz, 1945). He was one of the first researchers to use direct observation of human children as an experimental method for studying the importance of the early caregiving relationship, beyond the provision of physical needs, and his most significant contributions came from his studies on the effects of maternal and emotional deprivation. As part of his research in the 1930s, Spitz discovered that infants and children can die if they are not connected with or touched: that is, they can receive adequate nutrition and health care, but still fail to thrive without loving contact. Later on John Bowlby, a British psychologist, developed a theory which integrated such empirical findings with those from animal research into a model based on the concept of ‘attachment’. Attachment in this sense describes the emotional processes through which a caregiver regulates their child's arousal levels (Bowlby, 1958), and is defined as a deep and enduring emotional bond that connects one person to another across time and space (Ainsworth, 1979; Bowlby, 1969). Bowlby's attachment theory posits that infants have a universal need to seek close proximity with their caregiver when under stress or threatened, with the expectation of receiving protection and emotional support. Working alongside James Robertson in the 1930s, he observed that

children experienced intense distress when separated from their mothers, and even being fed by other caregivers did not alleviate the child's distress (Bowlby et al., 1952). These findings challenged the dominant theory of attachment at the time, which stated that children become attached to their mothers only because they are being fed (Dollard & Miller, 1950).

Bowlby's attachment theory is grounded in evolutionary theory and the concept of sensitive periods; i.e. periods of development during which the brain is particularly receptive to certain types of stimuli or experiences, and is thus more capable of adapting and reorganizing in response to experience; and experience-dependent mechanisms. It posits that infants are biologically pre-programmed to form attachments with others in order to increase their chances of survival (Bowlby, 1958). According to Bowlby's theory, infants form attachments with primary caregivers during a period between 0 and 30 months (2.5 years), which serves as a template for their future attachments to others, known as 'internal working models'. These attachments play a crucial role in shaping an individual's adult relationships and can have long-lasting effects on an individual's emotional and social development.

Mary Ainsworth, a developmental psychologist who conducted extensive research on attachment and attachment styles, supported and expanded upon John Bowlby's attachment theory (Ainsworth, 1967; Ainsworth & Bell, 1970). Ainsworth's research focused on the interactions between infants and their primary caregivers, and in which she developed the 'Strange Situation' protocol still widely used to observe and classify attachment styles in early development (Ainsworth et al., 1978). Different styles of interaction between infants and their primary caregivers can result in three types of attachment: secure, anxious-ambivalent, or anxious-avoidant (Ainsworth & Bowlby, 1991). Securely attached infants feel confident in their caregivers' availability and responsiveness, and enjoy exploring their environment. Anxiously-ambivalent infants are uncertain about their caregivers' availability and responsiveness, and become very anxious when their caregiver leaves. Anxiously-avoidant infants tend to dismiss their caregiver, and may avoid or resist physical contact and interaction with them. Ainsworth's work has had a lasting impact on the field of psychology, providing a foundation for understanding the role of attachment in the development of social and emotional skills and resilience in the face of adversity, and having deepened our understanding of the importance of early social experience in shaping an individual's development.



**Figure 2.** The 'Strange Situation' devised by Mary Ainsworth in the 1970s. This is a standardized procedure designed to observe attachment security in infants and young children within the context of caregiver relationships.

## Modern approaches

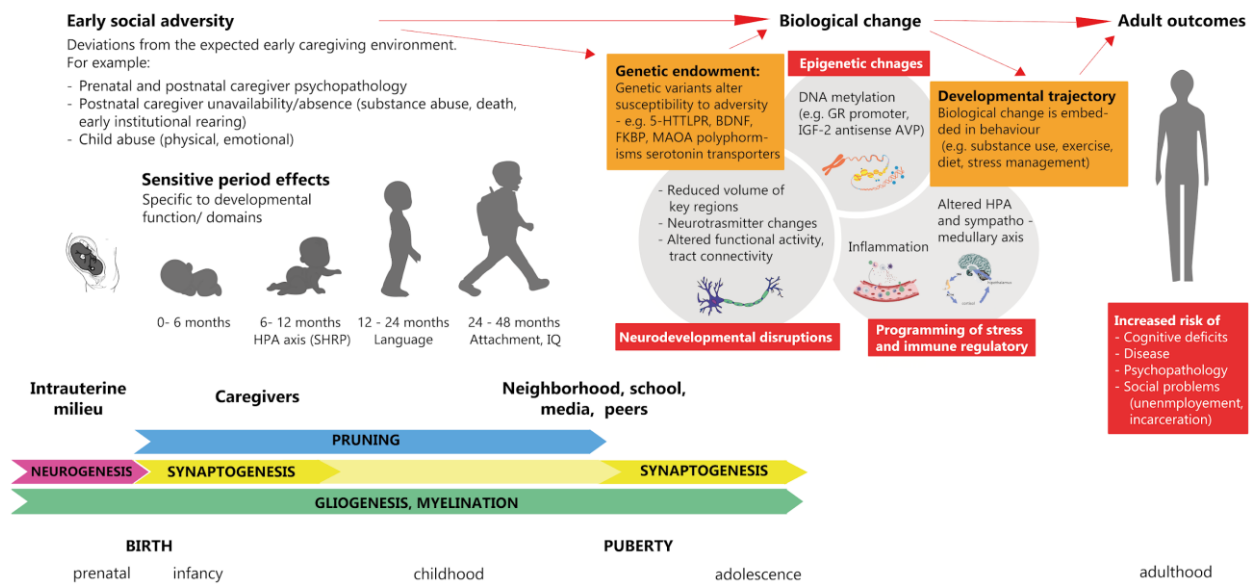
The literature reviewed so far sparked a keen interest in how the early environment, particularly early social experience, can influence specific aspects of development in primates (Cicchetti & Blender, 2006; Frankenhuis & Walasek, 2020; Thompson, 1998). While genetics clearly play a vital role in such development (Cloninger et al., 2019; Matute & Cooper, 2021), it is important to recognize that many environmental factors can also shape future structure and function during the first years of life in many crucial ways (Fox et al., 2010; Knudsen, 2004). A wealth of evidence now highlights the role of various factors, such as attachment and parenting practices, in shaping an individual's social and emotional development (Cicchetti & Blender, 2006; Denham & Brown, 2010; Tan et al., 2020). The 'expectable environment' during early development includes the emotional support and familiarity of a caregiver (Fox et al., 1994; Humphreys & Salo, 2020; McLaughlin et al., 2017; Morris et al., 2021; Nelson & Gabard-Durnam, 2020), with the further study of potential critical or sensitive periods for socio-cognitive and emotional development now vital for better understanding the impact of early social experience on specific developmental outcomes (Fox et al., 2010; Frankenhuis & Walasek, 2020).

The integration of social neuroscience with other fields such as developmental psychology, ethology, psychoanalysis, and psychiatry has greatly enhanced our understanding of the neural networks underlying the development of emotional, cognitive, and social behavior in primates. For example, researchers have used techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to examine functional brain activity during attachment behaviors, leading to the identification of specific brain regions and neural pathways involved, such as the the amygdala and ventral striatum (Ein-Dor et al., 2018; Mayes et al., 2005). Research has also elucidated the likely neural basis of other key social behaviors in primates, such as empathy, aggression, and social decision-making (De Waal & Preston, 2017; Gangopadhyay et al., 2021; Gold & Shadlen, 2007; Lischinsky & Lin, 2020; Paradiso et al., 2021). By combining insights from social neuroscience with those from other disciplines, researchers have been able to more fully comprehend the intricate relationship between genetics, environmental influences, and brain function in the development of such psychological processes. However, ***many questions remain regarding the mechanisms connecting specific aspects of early social experience with specific neurocognitive outcomes***, particularly in terms of typical versus atypical developmental trajectories and risk versus resilience.

## **Effects of early social adversity on development**

Over the past few decades, research concerning effects of early social experience on development has increasingly focused on how early social adversity (ESA) impacts different neural and psychological outcomes. ESA encompasses a range of experiences such as neglect and physical, sexual, or emotional abuse. These experiences involve violations in the early expectable environment, and can include factors such as increased social threat and a lack of expected social and cognitive inputs from primary caregivers (Holz et al., 2023; Malave et al., 2022; Katie A. McLaughlin & Sheridan, 2016; Wade et al., 2022). ESA in humans has been linked to later poor academic performance, occupational functioning, and social competence (Ford et al., 2011; Oeri & Roebbers, 2022; Sansone et al., 2012; Zielinski, 2009), as well as increased risk for psychiatric and substance use disorders (Dube et al., 2003; Gershon et al., 2013; Humphreys et al., 2020; Zeanah et al., 2009). Furthermore, increased prevalence of the neurodevelopmental disorder attention deficit/hyperactivity disorder (ADHD) has been

observed (Fuller-Thomson & Lewis, 2015; Golm et al., 2021; F. Tibu et al., 2016), as well as quasi autistic-like behaviours (Imai et al., 2021; Wilkinson et al., 2022). Growing evidence suggests that these poor outcomes arise via atypical development in related brain networks (e.g. Holz et al., 2023; McLaughlin et al., 2014), but much is still unknown about the actual links between these outcomes and changes in the brain across different stages of development.



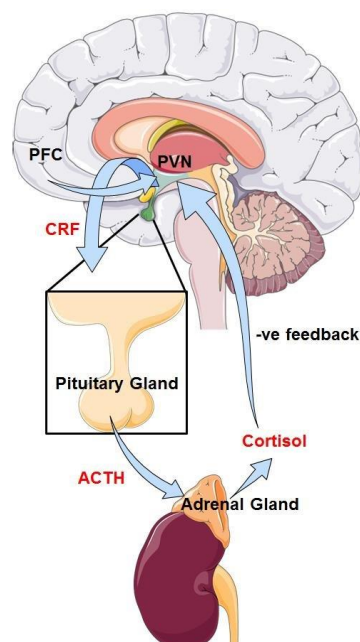
**Figure 3.** Neurobiological changes via which early social adversity (ESA) may lead to various poor outcomes. This figure was adapted from Nelson et al. (2020) and Ho & King (2021).

## Neurocognitive mechanisms underlying relationships between ESA and poor outcomes

There are several theories that have attempted to explain how ESA may affect neural development. ‘Stress response theories’ suggests that ESA can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a bodily system responsible for regulating the stress response (M. Gunnar & Quevedo, 2007; Loman & Gunnar, 2010). Chronic exposure to stress or trauma during early development can lead to changes in the way the HPA-axis functions, resulting in an overactive or underactive stress response (McEwen & Seeman, 1999). The stress response is a series of physiological reactions involving activation of the HPA-axis that occur when exposed to a stressor, such as physical injury, infection, or psychological stress. Once activated, the HPA-axis releases a cascade of glucocorticoid hormones, including



corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland, and cortisol from the adrenal glands. Cortisol, also known as the 'stress hormone', plays a central role in the body's response to stress. It helps to increase blood sugar levels, suppress the immune system, and regulate blood pressure, among other functions, which leads to the production of glucocorticoids. Glucocorticoids such as cortisol can easily cross the blood-brain barrier and bind to receptors in the hippocampus, prefrontal cortex (PFC), and amygdala. In particular, cortisol can bind to receptors in the PFC, and high levels of cortisol have been associated with impairments in PFC-dependent tasks, such as memory and decision-making. Chronic activation of the HPA axis and elevated cortisol levels have also been linked to structural and functional changes in the PFC, including reductions in the size and density of neurons (Kundakovic et al., 2015). However, these three brain structures (hippocampus, PFC, and amygdala) do not develop at the same rate in humans, and exposure to stress at different times during brain development may increase the risk of certain mental health disorders linked to differing brain circuitry (Raymond et al., 2018). Dysregulation of the HPA axis has been linked to increased risk for various mental health problems involving emotion dysregulation, including depression, anxiety, and post-traumatic stress disorder (Gunnar & Quevedo, 2007).

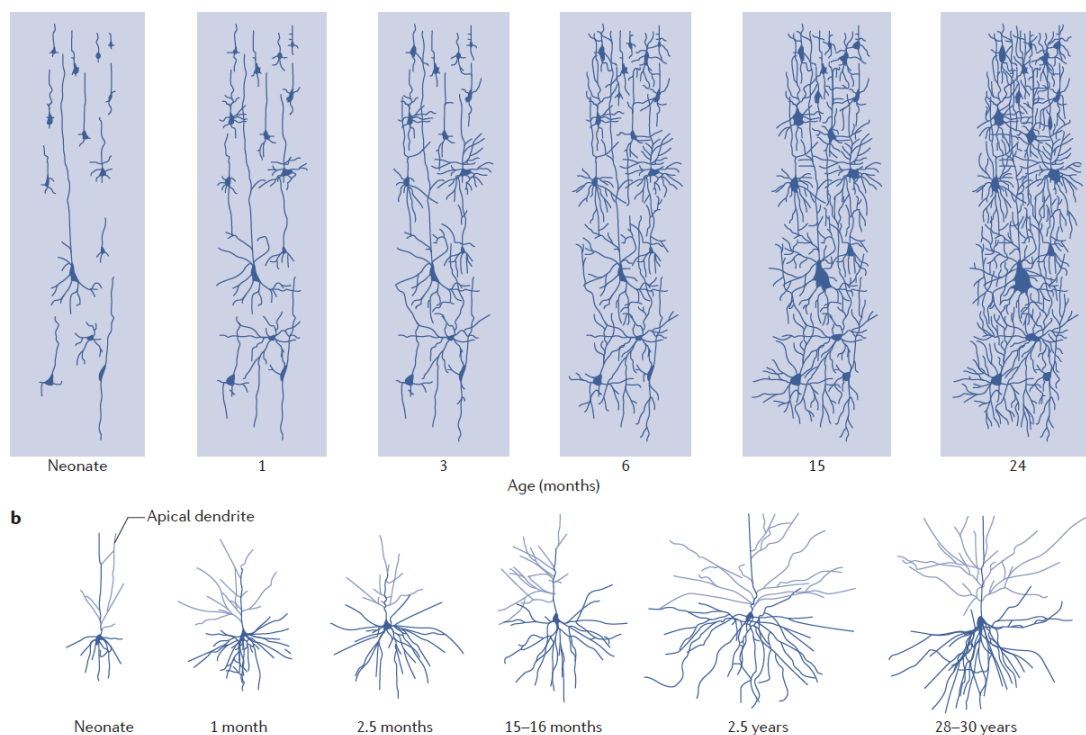


**Figure 4.** *Hypothalamic Pituitary Adrenal axis.* PFC = Prefrontal Cortex, PVN = Paraventricular Nucleus of the Hypothalamus, CRF = Corticotropin Releasing Factor, ACTH = Adrenocorticotropic Hormone (Figure from Papst, 2019).

Two main theories exist within the 'stress response' approach which attempt to explain the relationship between early adversity, HPA-axis dysfunction, and poor psychiatric outcomes later on: i) The 'stress sensitization' theory, which posits that early adversity leads to heightened reactivity to future stressors, increasing the risk of negative outcomes (McLaughlin et al., 2010); and ii) the 'stress inoculation' theory, which instead suggests that moderate levels of adversity may enhance resilience and protect against negative consequences, while extreme levels of adversity may increase later vulnerability (Parker & Maestriperi, 2011). Accordingly to such theories, chronic activation of the stress response system linked to early adversity may increase the risk of psychiatric disorders via different mechanisms such as allostatic load (Danese & McEwen, 2012; Guidi et al., 2021) and accelerated maturation (Callaghan & Tottenham, 2016). Allostatic load is the cumulative impact on the body of chronic stress, which can lead to allostatic overload when the body's coping mechanisms are exceeded (McEwen, 2005). Accelerated maturation refers to the 'speeding-up' of development in brain circuits that control emotion and reward/motivation, often interpreted as an adaptive response to early life stress. This accelerated development can manifest in the premature activation and closing of sensitive developmental periods in neural circuitry and its molecular composition in brain regions that control emotion expression, learning, and memory. While this may provide a short-term adaptive advantage, evidence suggest it can also have negative consequences on subsequent brain development, which can then have cascading effects on the brain that increase the risk of developing various psychiatric and behavioural problems in later life (Hanson & Chen, 2010; Herzberg et al., 2021).

Another theory highlights that ESA can lead to changes in the way the brain forms and maintains connections between neurons; i.e. neural plasticity (Ho & King, 2021; Miskolczi et al., 2019; Oginga et al., 2022). This is important for learning and memory, and is thought to be influenced by genetics, environment, and experience. When neural plasticity is disrupted by ESA, it may lead to differences in the way the brain processes and integrates information, resulting in higher-level cognitive problems such as problem-solving difficulties (Shonkoff et al., 2012). One mechanism through such effects on neural plasticity may occur is by disrupting the process of synaptic pruning, i.e. the elimination of unnecessary or weak connections between neurons (Kolb & Gibb, 2011). This process plays a key role in brain development and

the emergence of complex skills. Abnormal patterns of synaptic pruning may contribute significantly to the cognitive and behavioral problems linked to differences in the thickness and surface area of various cortical regions such as the prefrontal cortex (PFC) (Hodel et al., 2015; McLaughlin et al., 2014), the temporal cortex (Mackes et al., 2020; McLaughlin et al., 2014), the parietal cortex (Katie A. McLaughlin et al., 2014), and subcortical structures such as the hippocampus (Hanson & Chen, 2010; Hodel et al., 2015; Mehta et al., 2009; Sheridan et al., 2012; Nim Tottenham & Sheridan, 2010).



**Figure 5.** Increase and pruning of neuronal connections in an area of cortex across infancy until early adulthood. Figure from Gilmore et al. (2018).

Recently, several researchers have tried to integrate different mechanisms that may link ESA to poor specific poor outcomes in order to better understand the complex interactions between several factors that are likely central for the developing brain. ESA can have long-lasting effects on an individual's behavior, stress responses, and brain structure and function, particularly if it occurs during sensitive periods of development when crucial neural connections are being formed (Malave et al., 2022; Smith & Pollak, 2020). These effects may involve negative effects on several processes, including HPA-axis function, neurotransmitter systems, and processes such as neurogenesis, myelination, synaptogenesis, and synaptic pruning, and finally, modifications to stress-regulatory genes (Ho & King, 2021; Holz et al.,

2023; Malave et al., 2022). These changes can impact a wide range of brain regions and related connectivity involved in emotion processing, motivation, reward, memory, learning, and decision-making, which may all contribute in different degrees to overlapping and distinct social, cognitive, emotional, and behavioural outcomes. The timing of adversity within sensitive periods of development may also affect whether it influences experience-expectant or experience-dependent mechanisms, with infancy and early toddlerhood often being cited as particularly vulnerable periods in terms of early social experience impact (Gabard-Durnam & McLaughlin, 2020; Nelson & Gabard-Durnam, 2020b). Nevertheless, more research is now needed to elucidate more clearly the specific neural mechanisms linking ESA to increased risk for different outcomes (Holz et al., 2023; Smith & Pollak, 2020). This will be crucial for identifying the best targets for early intervention after exposure to ESA, and developing better treatments for psychopathologies and behavioural problems that have their roots in early life (Malave et al., 2022).

## **ESA and institutionalization: Effects of psychosocial deprivation on development**

Psychosocial deprivation in the form of early institutionalization is one model of ESA that has been of particular interest in the previous literature. Institutionalization refers to the long-term care of children in institutions, such as orphanages, rather than in family settings. Institutionalization has been associated with negative outcomes in numerous areas of development, including lower levels of physical growth, cognitive and language development (Kornilov et al., 2019), and increased rates of attachment disorders and other mental health problems such as mood disorders (van IJzendoorn et al., 2020).

The Bucharest Early Intervention Project (BEIP) is a randomized controlled trial investigating the effectiveness of foster care as an intervention for abandoned children placed in institutions as infants in Bucharest, Romania (Fox et al., 2017; Zeanah et al., 2003). The ongoing study includes comprehensive longitudinal assessments of 136 institutionalized children and their caregiving environments, with half having been randomly assigned to high-quality foster care and the other half remaining in institutional care. The average age of foster care placement was 22 months, with follow-up assessments occurring at 30, 42, 54 months,

8, 12, and 16 years of age, with assessments at later ages to come. Results so far show that, compared to a control group of never-institutionalized children, children raised in institutions exhibit significant delays in cognitive and motor development, language, and socio-emotional functioning, as well as higher rates of psychiatric disorders (J. Bick et al., 2017; Bos et al., 2011; Lamm et al., 2018; Nelson et al., 2019; Wade et al., 2022). Foster care was found to produce notable improvements in certain areas, but children in foster homes still lagged behind the control group in various aspects of development (Humphreys et al., 2022; Tibu et al., 2014).

To examine the neural underpinnings of how early social deprivation may have led to such poor socio-cognitive, emotional, and behavioural outcomes in institutionalized children, the project has utilized electroencephalography (EEG) and magnetic resonance imaging (MRI) to investigate differences in brain development among the Romanian orphans. At the baseline assessment at 22 months, using EEG, institutionalized children were found to have higher theta power but lower alpha and beta power compared to a never institutionalized control group (Marshall & Fox, 2004). This pattern of brain activity has been associated with ADHD, learning disorders, and other negative developmental outcomes (McLaughlin et al., 2010). At 12 years, previously institutionalized children also showed worse inhibition of planned action, which was associated with a larger P2 event-related potential (ERP) component and a smaller N2 component; the degree of neural activation moderated the association between ESA and externalizing symptoms (Lamm et al., 2018). Notably, alpha power in the foster care group and never institutionalized control group were comparable, whereas the institutionalized children continued to display reduced alpha power and greater theta power compared to the other groups even at 16 years (Debnath et al., 2020; Vanderwert et al., 2010, 2016). Reduced alpha power and elevated theta power suggest a deficit in cortical maturation in institutionalized children (Debnath et al., 2020). Reduced alpha power predicted worse executive function in adolescence (Wade et al., 2019a). In addition, by age 16, adolescents who had been in institutional care but were later placed in foster care showed greater mediofrontal theta cortical activity and better ability to adapt their behaviour after making mistakes compared to those who had experienced prolonged institutionalization (Buzzell et al., 2020). These findings suggest that high-quality foster care and a stable caregiving environment are important for improvement in the neural development of children who have previously experienced institutionalization (Buzzell et al., 2020; Debnath et al., 2020).

The use of MRI in this project also revealed that institutionalization can also lead to alterations in brain structure, including cortical thickness, white matter volume, and structural connectivity (Zeanah et al., 2017). Children who had been institutionalized had smaller brains overall, with reduced grey matter and white matter volume compared to controls (McLaughlin et al., 2014; Sheridan et al., 2012). A study by Sheridan et al. (2012) found that between the ages of 8 and 11 years, white matter in the cortex was reduced in children who had been institutionalized compared to those who had not. In a study using diffusion MRI to investigate structural connectivity, Bick et al. (Bick et al., 2017) found that at 8 years, children who had been institutionalized had higher levels of depression and anxiety compared to non-neglected children, which was not affected by early intervention. However, at 12 years, girls who received early intervention via foster care had reduced levels of internalizing symptoms, while boys did not show similar improvement (Bick et al., 2017). Notably, depression and anxiety symptoms at 8 and 12 years were linked to lower integrity in certain white matter tracts, and the integrity of these tracts indirectly affected the relationship between early rearing status and levels of internalizing symptoms. Specifically, the integrity of the external capsule and body of the corpus callosum were found to significantly moderate the link between early rearing and internalizing symptoms.



**Figure 6.** Romanian institution for abandoned children in 1991 (Figure from Carlén, 2017).

Recently, Sheridan et al. (2022) found that from age 9 to 16, children from this project raised in families from birth had thinner cortex in certain areas of the PFC (i.e. medial (mPFC), inferior frontal gyrus (IFG), temporal pole) compared to those exposed to institutional care, suggesting a long-term impact of institutional care on cortical development. Thinning in these areas was associated with externalizing psychopathology and impaired cognitive ability.

Institutionalization, randomization to foster care, and timing of placement were not related to subcortical volumes for any structure. The study also showed that the timing of placement into foster care and the length of time spent in institutional care were important factors in cortical development. In particular, children placed in foster care before 24 months of age had relatively thicker cortex in the middle frontal gyrus (MFG) in adolescence compared to those placed later, but thinner cortex in the anterior cingulate cortex (ACC) and IFG at 16 years. In addition, children exposed to institutional care had decreased white matter integrity in the superior longitudinal fasciculus (SLF), a tract that connects the lateral PFC to the parietal cortex, and which supports executive function and cognitive control, compared to those in foster care. In contrast, the foster care group had greater white matter integrity in the uncinate fasciculus, a tract that connects the inferior PFC with the amygdala and anterior temporal cortex, and is linked to emotion regulation.

The English and Romanian Adoptee (ERA) study is another longitudinal project examining the development of children adopted from Romania and placed in the UK in the 1990s (Rutter, 1998). According to current findings from this study, Romanian adoptees who spent less than six months in an institution had similar rates of ADHD, autism spectrum disorders (ASD), cognitive impairment, and excessive friendliness compared to UK control groups across most ages and outcomes. However, those who spent more than six months in an institution had higher rates of behaviours characteristic of ASD, disinhibited social engagement, and greater inattention and hyperactivity compared to control participants. Additionally, the group who spent more than six months in an institution had initially higher rates of cognitive impairment compared to controls, but these rates normalized in young adulthood. In contrast, self-rated emotional symptoms were quite comparable to controls during childhood and adolescence, but increased significantly by young adulthood (Sonuga-Barke et al., 2017). Another study found that early institutionalization was linked to impairment in various neuropsychological domains, including IQ, prospective memory, proactive inhibition, decision-making, and emotion recognition, in young adulthood (Golm et al., 2020). The study also found that the quality of the post-adoption home environment moderated the association between institutional deprivation and neuropsychological outcomes in adulthood, with better post-adoption environments leading to better outcomes. Finally, this study also demonstrated that children with a history of psychosocial deprivation

had a higher prevalence of mood disorders, with the severity of these disorders being linked to the duration of deprivation (Golm et al., 2020). Mackes et al. (2020) followed-up this finding, showing that being exposed to early deprivation during the first years of life was related to significantly smaller total brain volumes and was negatively associated with the duration of deprivation in adulthood. The reduction in total brain volume mediated the relationship between institutionalization and lower IQ and higher ADHD symptoms. Deprived adult adoptees had lower right inferior frontal cortex surface area and volume, but higher right inferior temporal lobe thickness and volume compared to the control group. The increase in right inferior temporal volume in deprived individuals was associated with lower levels of ADHD symptoms. Deprivation duration was positively associated with right mPFC volume and surface area. They found no effects of deprivation on subcortical brain volume in the adult sample (e.g. amygdala and hippocampus). These findings suggest that limited severe deprivation during the early years of life is associated with lasting changes in adult brain structure, even when there is extended enrichment in adoptive homes later in childhood (Mackes et al., 2020).

The International Adoption Project in the United States, launched in 1999 by Megan Gunnar and her team, also focused on the impact of early institutionalization on development. The project involved analysis of a registry of 6,000 children adopted by families in the USA from institutions abroad. Post-institutionalized children were found to struggle with executive function, including cognitive flexibility, inhibitory control, and working memory, and perhaps experienced delays in theory of mind development; i.e. the ability to understand the mental states of others (Gunnar et al., 2007; Gunnar et al., 2001). Certain differences in brain development, including a reduction in total brain volume and changes in the development of the PFC and hippocampus (Hodel et al., 2015) were proposed to underlie these difficulties.

Although a number of studies from the projects above failed to find effects of early institutionalization on subcortical structures, other research suggests that psychosocial deprivation does affect subcortical development. A longitudinal study by VanTieghem (VanTieghem et al., 2021) found that institutionalization was associated with reduced hippocampal volume and reduced growth rate of the amygdala in children, as well as smaller hippocampal and amygdala volume in adolescence. Tottenham and colleagues (2011) also found increased amygdala activity measured using fMRI during an emotional Go-No-Go task



only in post-institutionalized children, which was inversely related to the amount of eye-contact made during the task. Callaghan et al. (2019) also found decreased amygdala reactivity to parental cues which predicted reduced anxiety in previously institutionalized adolescents. The engagement of a broader prefrontal-subcortical circuit in post-institutionalized older children and adolescents has been shown to contribute to their aversive learning compared to a control group, with increased connectivity between the hippocampus and the ventromedial prefrontal cortex related to improvements in anxiety in the post-institutionalized group (Silvers et al., 2016). Interestingly, Silvers et al. (2017) also found that although individual differences in vigilant behavior were positively correlated with amygdala responses to fearful and happy faces in all youths, the degree to which amygdala responses were stronger for fearful versus happy faces was associated with greater anxiety in previously institutionalized youths only. However, other studies part of the BEIP found no differences between never institutionalized and institutionalized children in terms of emotional face processing, including neural correlates of facial emotion processing (Jeon et al., 2010; Young et al., 2017). Finally, Fareri et al. (2017) found that stronger coupling between the ventral striatum and the mPFC was associated with parent-reported social problems in previously institutionalized adolescents, and differences in resting-state connectivity between these two brain regions increasingly affected social behaviors, particularly during adolescence.

Some recent theories concerning the effects of ESA on brain development have attributed more focus to the striatum than previous ones. Along with the PFC, amygdala and hippocampus, which form important components of the stress system, the striatum has been posited as part of a regulatory mechanism that can also be disrupted by psychosocial adversity (Fareri et al., 2017) and interacts with the stress system. In particular, it is hypothesized that changes in fronto-striatal circuitry following psychosocial deprivation may have an important role in the emergence of poor emotion regulation and executive function (Behen et al., 2009; Bick & Nelson, 2015; Eluvathingal et al., 2006). In addition, studies focusing on alterations in reward processing in the context of early institutionalization highlighted the key role of fronto-striatal network (Goff et al., 2013; Herzberg & Gunnar, 2020). However, only few studies so far have considered the role of the striatum explicitly (e.g. Fareri et al., 2017; Bick et al., 2017), and more research is needed to elucidate how this subcortical structure and its connectivity may contribute to negative outcomes after exposure to psychosocial deprivation.

To summarize, studies of psychosocial deprivation have consistently revealed effects of early and prolonged exposure to deprivation, in the form of institutionalization, on the development of the PFC and other cortical regions using different measures of brain structure, including cortical thickness and surface area. These changes in the PFC are linked to negative outcomes, including impaired executive function and increased risk for psychopathology. However, there is inconsistency in findings concerning the effects of institutionalization on subcortical development, such as the amygdala, hippocampus, and striatum, though a number of studies have linked connectivity of these regions to institutionalization. Additionally, only a few studies thus far have looked at functional or structural connectivity after institutionalization, and importantly, most of these studies focus on only one age of assessment, and measures are often not looked at concurrently. *Altogether, this limits our understanding of the aspects of neural development linking institutionalization to specific poor outcomes.*

**Table 1.** Summary of the longitudinal effects of early institutionalization found in the studies presented in this section of the chapter.

Project	Group (compared to control)	Developmental outcomes			
		<i>Behaviour</i>			
		Infancy	Child	Adolescent	Adult
<b><u>Bucharest Early Intervention Project (BEIP)</u></b>	Institution	Lower IQ	Lower IQ and deficits in attention, spatial planning and problem solving, short-term visual memory, working memory, verbal comprehension, processing speed, reward responsivity	Deficits in attention, spatial planning and problem solving, working memory and new learning, inhibition of planned action, reward responsivity	Lower IQ and deficits in verbal comprehension, processing speed, working memory, perceptual reasoning

		Higher levels of psychiatric symptomatology including depression, anxiety, attachment disorders, emotional reactivity, self-control	Higher levels of psychiatric symptomatology including externalizing and internalizing symptoms, worse self-control, ADHD, and blunted reactivity to social stress	
Adopted	Lower IQ	Lower IQ and deficits in attention, spatial planning and problem solving, short-term visual memory, verbal comprehension, and processing speed	Deficits in attention, spatial planning and problem solving, and short-term visual memory	Lower IQ and deficits in verbal comprehension, processing speed, working memory, and perceptual reasoning
		Higher levels of psychiatric symptomatology including depression, anxiety, and worse self-control	Higher levels of psychiatric symptomatology including ADHD	
<b>Brain</b>				
	<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>
Institution	Higher theta power, lower alpha and beta power	Higher theta power, lower alpha power	Higher theta power, lower alpha power	
		Smaller brains overall, reduced white matter and grey matter volumes	Thicker cortex in medial PFC (mPFC), inferior frontal gyrus (IFG), temporal pole, and decreased white matter integrity in the superior longitudinal fasciculus (SLF)	

	Adopted	Higher theta power, lower alpha and beta power	Smaller brains overall, reduced white matter and grey matter volumes	Thicker cortex in medial (mPFC), inferior frontal gyrus (IFG), temporal pole	
<b><u>English and Romanian Adoptee (ERA) study</u></b>	<b><i>Behaviour</i></b>				
		<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>
	Adopted (more than 6 months in institutions)		Higher rates of cognitive impairment	Higher rates of cognitive impairment	Lower IQ and deficits in prospective memory, proactive inhibition, decision-making
			Higher prevalence of ASD, disinhibited social engagement, ADHD	Higher prevalence of ASD, disinhibited social engagement, ADHD	Deficits in emotion recognition and higher rates of emotional symptoms and mood disorders
	<b><i>Brain</i></b>				
		<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>
	Adopted (more than 6 months in institutions)				Smaller total brain volumes, smaller inferior frontal cortex, and bigger inferior temporal lobe, including thicker cortex
<b><u>International Adoption Project</u></b>	<b><i>Behaviour</i></b>				
		<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>
	Adopted (12 months in institutions)		Deficits in cognitive flexibility, inhibitory control, and working memory		

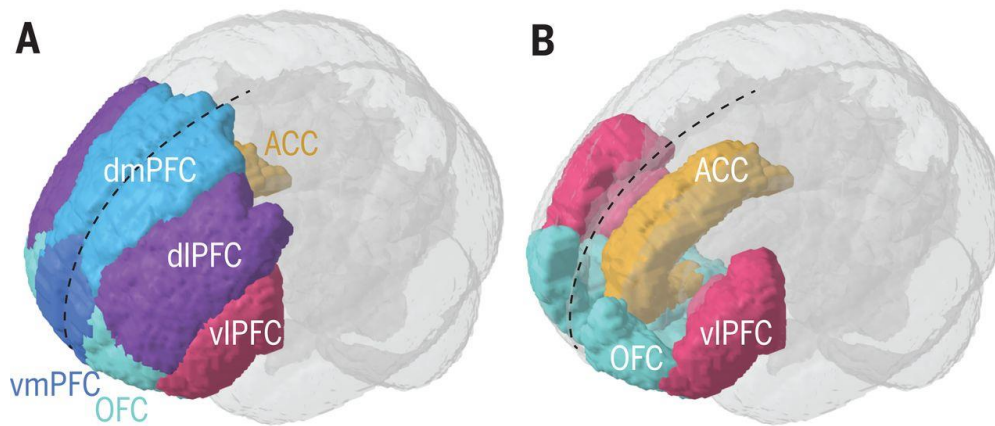
			Increased risk of attention problems, and social problems			
	<b>Brain</b>					
		<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>	
	Adopted (12 months in institutions)			Smaller total volume in PFC and hippocampus		
<b>Other studies</b>	<b>Behaviour and brain</b>					
		<b>Infancy</b>	<b>Childhood</b>	<b>Adolescence</b>	<b>Early adulthood</b>	
	Post-institution			Smaller hippocampal and amygdala volume		
				Increased amygdala activity in response to fearful faces (and emotional tasks in general) and related to increased anxiety and less eye contacts		
				Decreased amygdala reactivity to parental cues related to less anxiety		
				Higher hippocampal-frontal connectivity related to less anxiety		
				Higher fronto-striatal connectivity related to increased social problems		
				Broader prefrontal-subcortical circuit related to higher aversive learning		

## Early institutionalization and self-regulation

Critically, many of the adverse psychological and behaviour outcomes discussed so far in the context of psychosocial deprivation are linked to problems of ‘self-regulation’. Self-regulation is the flexible regulation of cognition, behaviour, and emotion (Calkins & Perry, 2016), with poor self-regulation linked to poor academic and social functioning, criminal behaviour (Bridgett et al., 2015; Distefano et al., 2021; Eisenberg et al., 2010), and several psychiatric and neurodevelopmental disorders (Ip et al., 2019; Lochman, 2009; Nigg, 2017). For example, research has shown that difficulties with self-regulation in childhood can lead to

lower income and educational attainment by adulthood (McClelland et al., 2014, 2015). Self-regulation can be separated into two distinct, but interacting components: i) "top-down" self-regulation, which reflects processes requiring more effortful and executive control, which help to resolve conflict or prepare for an anticipated goal; and ii) "bottom-up" self-regulation, which reflects processes that are more automatic and stimulus driven. "Top-down" self-regulation has also been further divided into behavioural and emotional self-regulation, while "bottom-up" self-regulation has been divided into behavioural inhibition/fear and impulsivity (Bridgett et al., 2015).

In terms of top-down processes, behavioural constructs of self-regulation include effortful control, cognitive control, and executive function, which although often discussed in the literature as distinct entities, are starting to be viewed as similar or overlapping processes, at both conceptual and behavioural levels (Bridgett et al., 2015). These involve the modification of attention, memory, or working memory to try and enhance adaptation or achieve a goal, thus accounting for top-down aspects of self-regulation at the cognitive level (Nigg, 2017). These self-regulation constructs also overlap at the neurobiological level, with several regions of the brain such as the dorsal ACC, dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), orbitofrontal cortex (OFC) being associated with these various self-regulatory processes (Berger, 2011; Posner et al., 2012; Wager, 2014) (Figure 7). For clarity, from now on in this thesis, the term executive function will be used to refer to the cognitive dimension of the self-regulation construct. Emotional self-regulation has been studied primarily in the context of specific emotion regulation strategies such as reappraisal and suppression (Boemo et al., 2022; Ellis et al., 2019; Kelley et al., 2019). Reappraisal involves cognitive reframing of emotions, while suppression reduces outward expression of emotions (Gross & John, 1998). Studies show that reappraisal and suppression are associated with activation of the dlPFC, vlPFC, dorsal mPFC, ACC, and other areas in the frontal lobe (Buhle et al., 2014; Cutuli, 2014; Goldin et al., 2008) (Figure 7).

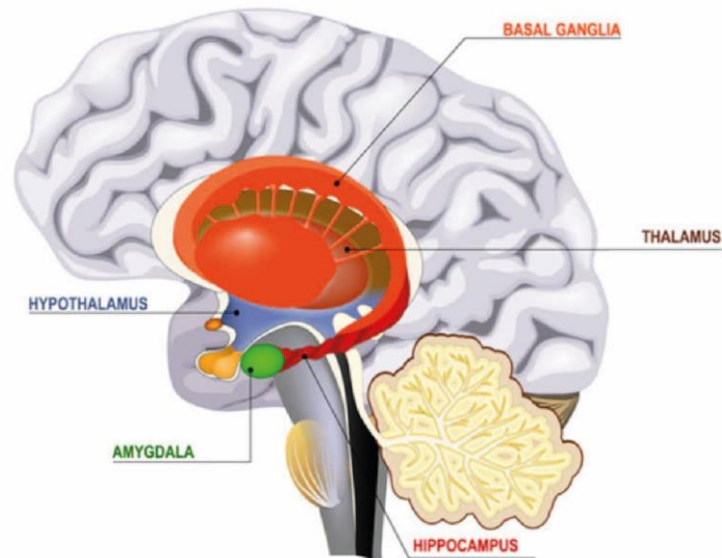


**Figure 7.** *Anatomical subdivision of prefrontal cortex (PFC).* These regions of the frontal lobe are primarily involved in both cognitive and emotional top-down self-regulation processes. dmPFC = dorsomedial PFC; ACC = anterior cingulate cortex; dlPFC = dorsolateral PFC; vmPFC = ventromedial PFC; OFC = orbitofrontal cortex; vlPFC = ventrolateral PFC. Figure from Carlén et al. (2017).

In terms of bottom-up processes, behavioural inhibition/fear as well as avoidance represents a reactive and "over-controlled" type of self-regulation, where individuals tend to be more cautious and reserved in novel situations, and are more likely to be fearful. Research shows that the subcortical structures most consistently associated with behavioural inhibition/fear are the amygdala and hippocampus (Kennis et al., 2013), but also the striatum (Ide et al., 2020). Impulsivity, on the other hand, is a reactive, uncontrolled type of self-regulation, characterized by acting without much forethought or consideration of the long-term implications of behaviour (Bridgett et al., 2015). The neural areas often associated with impulsive behaviours include the ventral striatum, specifically the caudate nucleus, nucleus accumbens, and putamen (Besson et al., 2010; Whelan et al., 2012).

Previously, top-down and bottom regulation processes have been viewed rather separately, with top-down self-regulatory processes appearing to originate largely in neural structures of the frontal lobes and ACC, and bottom-up self-regulation processes apparently served more by subcortical structures. However, increasing attention has been given to integration across different aspects of self-regulation. Specifically, the distinction between bottom-up and top-down self-regulation is no longer commonly viewed as absolute but rather on a continuum (Nigg, 2017). These two systems are not mutually exclusive, but instead interact through successive reciprocal neural feedback loops. For example, top-down systems can affect bottom-up responses by activating, suppressing, or biasing them, while bottom-up systems can also activate goal-related behaviour through priming or other effects, which in

turn can limit the effects of top-down processes (Avital-Cohen & Tsal, 2016; Verbruggen et al., 2016). This highlights the complex and dynamic nature of self-regulation and its underlying neural mechanisms, and the importance of considering brain connectivity and interactions between different circuits rather than neural single structures only.



**Figure 8.** *Subcortical regions forming part of the limbic system.* These subcortical regions are primarily involved in bottom-up self-regulation processes. Note, the basal ganglia includes the striatum (Figure from News medical life sciences; Designua / Shutterstock).

Previous research framing differences in development in terms of self-regulation has shown that adverse early social experience is associated with deficits in self-regulation during childhood (Bridgett et al., 2015; Evans & Kim, 2012; Hostinar et al., 2012). This is linked to outcomes such as indiscriminate friendliness and problems in regulating affect in young adults who experienced early institutionalization (Kennedy et al., 2017). Additionally, much evidence has been provided for early psychosocial deprivation increasing risk for ADHD symptoms (Loman et al., 2013; Pollak et al., 2010; Roy et al., 2004; Rutter et al., 2001; M. Sheridan et al., 2010; Wiik et al., 2011), a disorder characterized by self-regulatory difficulties. However, findings are not entirely consistent across studies, with the common use of teacher or parental reports, questionnaires, and different ages of assessment likely contributing to this. Furthermore, very few studies have assessed differences in both psychological and related brain development concurrently. Recent theories have proposed that stress physiology may act as a primary mechanism linking early experiences of adversity to reduced self-regulatory



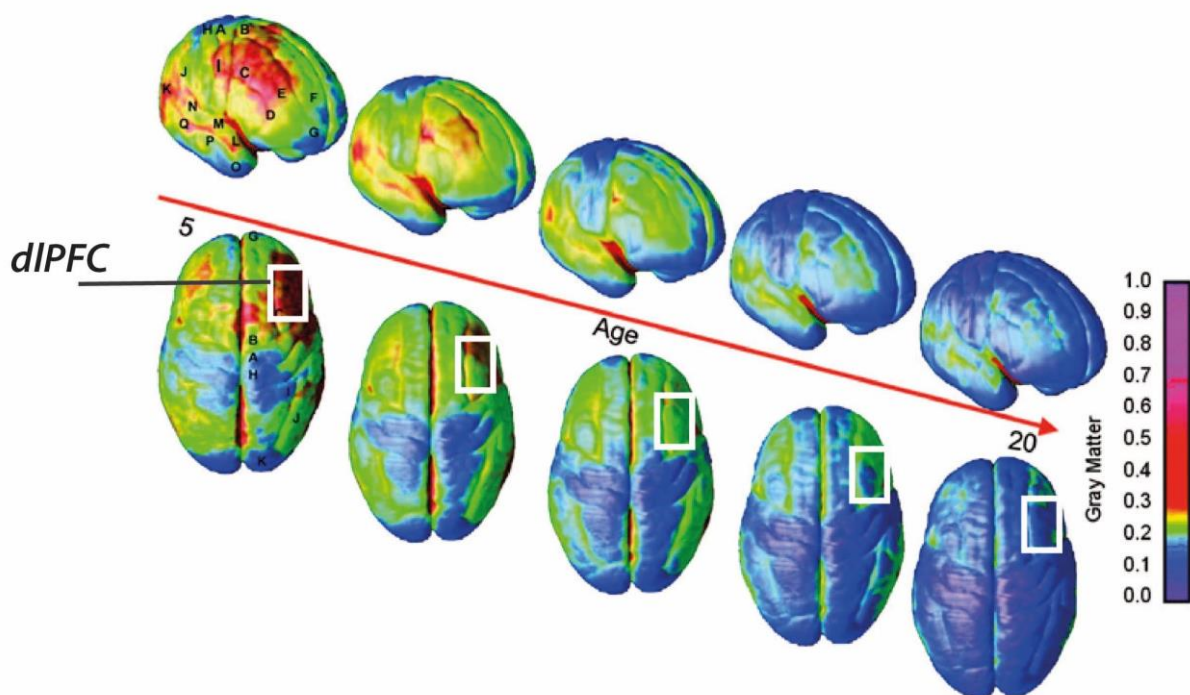
abilities (Raymond, 2018), with adversity-related alterations in brain regions such as the hippocampus, amygdala, and PFC following ESA (Lupien et al., 2009; McCrory et al., 2011). Therefore, impairments in the development of PFC, which plays a crucial role in the control of behaviour, cognition, and emotion, supporting self-regulation mechanisms, may underlie deficits in various aspects of self-regulation abilities across development (Miller & Cohen, 2001; Nigg, 2017). Notably, recently research has also considered how poor executive function may contribute to risk factors associated with self-regulation difficulties specifically in the context of early psychosocial deprivation (Hofmann et al., 2012), with PFC and PFC-subcortical networks also playing a central role in executive function (Adele Diamond, 2011; Friedman & Robbins, 2022).

It is now essential to integrate research on emotional and cognitive processes involved in self-regulation in order to gain a more comprehensive understanding of the complex mechanisms underlying this (Nigg, 2017; Pruessner et al., 2020). This is especially true in the context of ESA, where many poor outcomes may arise from effects on emotional and cognitive processes, as well as their interaction and overlapping features. For example, studies have shown that a higher level of executive function is associated with successful emotion regulation, and that the implementation of emotion regulation strategies correlate with individual differences in executive function, including the ability to inhibit prepotent responses, update information in working memory, and shift mental sets (Gross, 2015; Joormann & Tanovic, 2015). However, ***research on these two dimensions are very rarely looked at jointly, and research focused on the role of cognitive factors in poor outcomes seen in the context of ESA is currently lagging behind that of emotional processing*** in general.

## **Adolescence as a sensitive period of development after psychosocial deprivation**

The timing and duration of sensitive developmental periods is likely influenced by evolutionary constraints, stress, and attachment style (Opendak et al., 2017). Sensitive periods in infancy have been linked to changes in HPA-axis function and neural plasticity, and are commonly associated with effects on development of the amygdala, hippocampus, and PFC (Ho & King, 2021). Although much research on sensitive periods has focused on infancy and

early childhood, interest in potential sensitive periods beyond the earliest stages of development is growing. In particular, adolescence is increasingly being considered as a particularly important sensitive period later in development (Frankenhuis & Walasek, 2020; Fuhrmann et al., 2015; Larsen & Luna, 2018). This period is marked by significant physical, cognitive, and emotional changes, including substantial refinement of self-regulatory processes (Casey, 2015; Cohen et al., 2016; Nigg, 2017) and marked development in the PFC (Spear, 2016). As well as changes in PFC regions, important modifications in connectivity of the PFC also take place during adolescence. This includes development in fronto-limbic and fronto-striatal circuits (Ojha et al., 2022), which are thought to play a significant role in the refinement of executive function and emotion regulation processes during adolescence (Baker et al., 2022; Darki & Klingberg, 2015; Ojha et al., 2022). Relatedly, adolescence is also a time of increased risk-taking and experimentation, which may be impacted negatively by effects of ESA on emotional and social development (Andersen et al., 2021).



**Figure 9.** PFC development from childhood to adulthood. Development in dIPFC, which plays an important role in executive function refinement, is highlighted. Right lateral and top views of the dynamic sequence of grey matter maturation over the cortical surface. In red/yellow are the parts of the brain less fully mature; in blue/purple are the parts of the brain more fully mature (Figure adapted from Gogtay et al., 2004).

The concept of 'sleeper effects' in development refers to the delayed manifestation of early experiential impact, and may contribute to poor outcomes emerging in adolescence after exposure to ESA. This phenomenon, also referred to as an "incubation period" (Lupien et al., 2009), suggests that early experiences in infancy and early childhood may not affect certain aspects of development until later on in life, and may interact with prolonged stressors that accumulate over time (Sapolsky, 1996; Sapolsky et al., 2000). Evidence of sleeper effects has been found in a variety of domains, including face processing (Maurer et al., 2007), visual processing (Maurer et al., 2007), behavioural disturbance, executive function, and socio-emotional development (Maurer et al., 2007). For example, in the context of ESA, individuals who experienced maltreatment in childhood may not demonstrate a negative impact of this experience until later on in life, in the form of reduced hippocampal volume (which has a protracted developmental time-course) linked to externalizing psychopathology (Woon & Hedges, 2008; Zeanah et al., 2009). This underscores the importance of considering later sensitive periods and sleeper effects in future longitudinal studies of ESA, especially during adolescence, with further research now needed to fully understand the mechanisms underlying these phenomena.

Despite psychosocial deprivation being a form of ESA that appears most closely connected to atypical aspects of self-regulation such as executive function (Johnson et al., 2021), and that evidence suggests that adolescence is a sensitive period for the executive function development (Thompson & Steinbeis, 2020), ***very little is known about the trajectory of executive function development and its underlying neural correlates across adolescence after exposure to early deprivation.*** In a rare longitudinal study (Wade et al., 2019) examining the impact of institutionalization on cognitive development in children and adolescents, early-emerging deficits in attention, short-term visual memory, spatial planning, and problem solving were apparent in children who had been institutionalized versus those who had not. These differences remained consistent throughout adolescence, with the gap in spatial working memory between ever- and never-institutionalized children actually increasing by adolescence. However, the study also revealed that other early difficulties in visual-spatial memory displayed by children in foster care were mitigated by adolescence. Such findings suggest that early psychosocial deprivation may have varying effects on cognitive

development depending on the specific skill being evaluated and whether or not they were later placed in a supportive family environment.

## **Macaque model of early psychosocial deprivation**

Macaques have often been used as a non-human primate model for studying the effects of ESA on development because they share many similarities with humans in terms of their social, cognitive, and emotional development, and physiological and genetic characteristics (Phillips et al., 2014; Rosati et al., 2016; Sallet, 2022; Wang et al., 2020; Xue et al., 2016). Like humans, macaques are highly social animals and their social relationships can have a significant impact on their development and well-being (Cooper et al., 2022). Self-regulatory behaviours are also clearly demonstrated by macaques, including executive function and affective regulation (Machado & Bachevalier, 2003; Miller et al., 2019). Furthermore, macaques have very similar brain organization and development to that of humans, making them a good model for studying effects of early social experience on brain development (Balint et al., 2021; Kim, 2022; Schumann et al., 2019). Another advantage of the macaque model is that researchers can more easily use more objective methods to assess developmental outcomes (e.g. via behavioural observations); for example, in humans, often self-report measures (e.g. questionnaires) are utilized in isolation. Another advantage of using a macaque model is the possibility to better control variables in the early social environment, which allows for more precise experimental control than is possible in human studies. This makes it easier to identify the specific effects of ESA on various aspects of development and behaviour. Finally, macaques have a shorter developmental time-frame than humans, allowing researchers to conduct longitudinal studies in a relatively shorter time period compared to humans, and assessment of various aspects of brain development is more feasible.

Several studies have investigated the effects of early psychosocial deprivation in macaques on behavioural development. These studies have exposed macaques to rearing conditions involving caregiver absence, such as being separated from their mothers for extended periods of time or being reared by human experimenters in a nursery of peers (Balint et al., 2021; Kim, 2022; Schumann et al., 2019). Early psychosocial deprivation appears to have

a negative impact on many aspects of macaque development, similar to humans, including increased sensitivity to threat, anxiety, aggression, impaired social relationships, and motor function (Balint et al., 2021; Kim, 2022; Schumann et al., 2019). Most research has focused on earlier stages of macaque development, though the little that has focused on the later juvenile period or adulthood does suggest long-lasting effects of early deprivation (Corcoran et al., 2012; Dettmer & Suomi, 2014; Zhang et al., 2016).

There have not been many studies on the effects of early psychosocial deprivation on brain development and related poor outcomes in macaques, but there is some evidence that this is associated with changes in brain structure and function. This includes altered dendritic arborization and synaptic signalling in the PFC, hippocampus, and amygdala (Coplan et al., 2014; Howell et al., 2014; Provençal et al., 2012; Sabatini et al., 2007; Siegel et al., 1993; Spinelli et al., 2009). These brain areas are an important part of fear circuitry, and as previously noted, play a crucial role in HPA-axis regulation (Kalin et al., 2007; McKeon et al., 2022; Raper et al., 2013). A few EEG studies also suggest that early deprivation is associated with abnormal cortical activity in attention and sensorimotor regions in response to social stimuli (Festante, Rayson et al., 2021; Vanderwert et al., 2015). These changes may contribute to the behavioural and cognitive changes observed in macaques exposed to early psychosocial deprivation, however, like in humans, more research is needed to elucidate the neurocognitive mechanisms linking early deprivation to specific poor outcomes later in life.

Using another macaque model of ESA, maternal abuse, a couple of studies have investigated the effects of infant maltreatment in rhesus monkeys on development of white matter tracts involved in socioemotional behaviour using diffusion MRI (Howell et al., 2019). Early maternal abuse was associated with reduced structural integrity in certain white matter regions, including the corpus callosum, occipital white matter, external medullary lamina, and brainstem in adolescent macaques (Howell et al., 2013). These changes were suggested to reflect reduced myelination, and were also associated with elevated cortisol levels and increased social aggression. In another study, the same group found that white matter integrity increased longitudinally from the infant to early juvenile period, consistent with human findings and other primate work (Barnea-Goraly et al., 2005; Kubicki et al., 2019; Lebel et al., 2019). In addition, they found a decrease in the structural integrity of the middle longitudinal fasciculus and the inferior longitudinal fasciculus in maltreated animals, with

these tracts thought to be associated with motivational valence, social learning, and social interactions ( Howell et al., 2019).

Very few studies have examined the effects of psychosocial deprivation on cognitive functioning in macaques, despite this likely playing a crucial role in risk or resilience for many adverse outcomes seen in the context of deprivation. One study by Sánchez et al. (1998) demonstrated that infant macaques reared individually in a nursery had impaired cognitive functioning (i.e. spatial learning and memory) compared to infant macaques reared in normal conditions. However, in another study (Murphy & Dettmer, 2020), infant macaques reared in a nursery of peers did not show any differences in reward association, cognitive flexibility, or impulsivity compared to macaques reared in typical conditions when they reached adulthood. These inconsistent findings suggest that the effects of early psychosocial deprivation on cognitive functioning in macaques is complex, and that findings likely depend on the measures of cognitive functioning used, and we do not know about cognitive development later on. Overall, these studies provide strong evidence that early psychosocial deprivation in macaques likely impacts many aspects of social, emotional, and cognitive development. However, ***much is still unknown about the neural mechanisms linking early deprivation to specific outcomes in macaques or different trajectories of development after ESA exposure, especially in terms of cognitive development.***

## **This thesis**

Clearly, many questions remain about the neurocognitive mechanisms linking early psychosocial deprivation to specific poor outcomes across different periods of development. Notably, adolescence is a time where huge developments in executive function take place, which has been identified as a key predictor of academic, socio-emotional, and occupational success, and psychiatric health. This is proposed to rely on a sensitive period of brain development, characterized by significant maturation of the PFC, as well as its connectivity with other regions such as the striatum. By studying the effects of early psychosocial deprivation in macaques, a nonhuman primate species with neurocognitive structure and function similar to humans, we can gain a better understanding of these mechanisms, which could inform the development of interventions and prevention strategies to ameliorate

difficulties experienced by those exposed to early psychosocial deprivation. This type of research has the potential to not only improve understanding of the impact of early life experiences on brain development, but also how to promote healthy development and prevent negative outcomes in later life after exposure to ESA.

Based on some of the knowledge gaps highlighted here, **this thesis** aimed to address the following **two research questions: a)** how does early psychosocial deprivation influence executive function in macaques across adolescence into early adulthood; and **b)** what are the neural mechanisms linking early psychosocial deprivation to poor executive function? To answer these, the **two core objectives** were: **i)** to investigate the longitudinal and long-term effects of psychosocial deprivation on macaque executive function, as well as working memory and inhibitory control components of executive function specifically; and **ii)** identify aspects of structural brain development in PFC as well as fronto-parietal and fronto-striatal circuitry that may underlie differences in executive function after psychosocial deprivation.

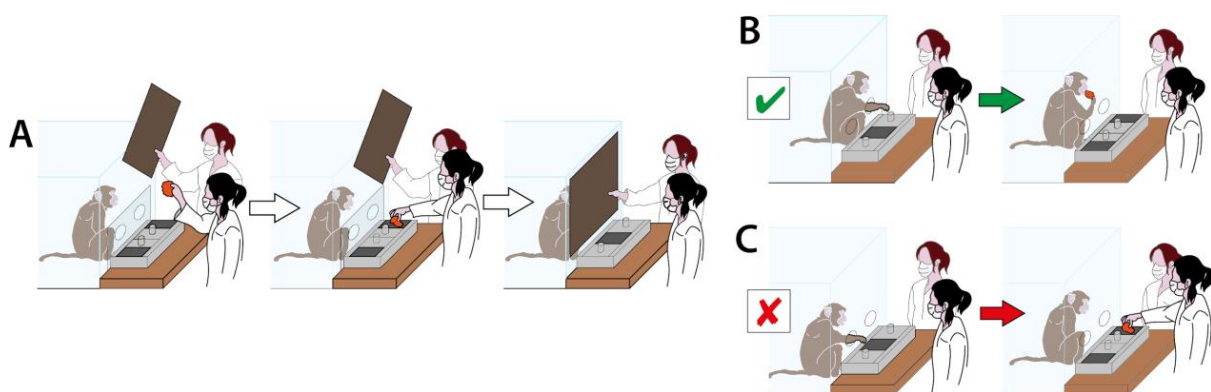
To achieve these objectives, a standardized behavioural task was used to assess executive function at two time-points corresponding to adolescence and adulthood in two groups of macaques (one peer-reared, one mother-reared). At the same time-points, MRI (anatomical and diffusion) data were acquired in order to assess cortical thickness and white-matter integrity in executive function-related brain circuitry. **Results are presented in Chapters 3 and 4** of this thesis, which are outlined briefly below. The studies presented in these chapters are part of a wider project investigating the effects of early psychosocial deprivation on multiple aspects of macaque development. This is the first longitudinal project looking at the effect of early psychosocial deprivation on the development of both brain and behaviour in rhesus macaques across adolescence. The methodology of this wider project is described in **Chapter 2**.

### ***Study 1: Longitudinal effects of early psychosocial deprivation on macaque executive function: Evidence from computational modelling***

In **Chapter 3** a paper that has been accepted for publication in a peer-reviewed journal (Massera et al., *in press*) is presented. In this paper, we asked what the longitudinal effects of early psychosocial deprivation might be on executive function in rhesus macaques across adolescence into early adulthood, assessed behaviourally using an 'A-not-B' task (Diamond &

Goldman-Rakic, 1989; Holmboe et al., 2018). The use of this task allowed for the assessment of both general executive function performance, and via the fitting of a computational model of decision-making, the assessment of specific components of executive function.

It was *hypothesized* that: *i)* early psychosocial deprivation will be negatively associated with general executive function; *ii)* that negative effects of early deprivation on executive function will persist across adolescence into adulthood; and *iii)* animals exposed to early deprivation will show specific deficits in working memory and inhibitory control.



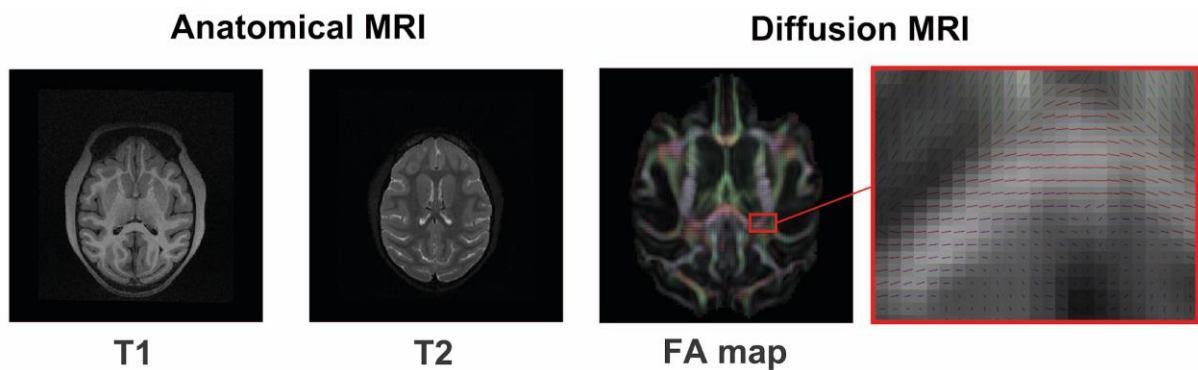
**Figure 2.** *Task procedure.* The series of images illustrates the sequence of a single trial. In the first three images (A) Experimenter 1 shows the food to the subject, places it in the well, and Experimenter 2 blocks the vision of the subject during the delay period. The top right images (B) illustrate a ‘correct’ choice, with the subject reaching for the well where the food was hidden and then eating the food. The bottom right images (C) illustrate an ‘incorrect’ choice, with the subject choosing the well containing no food and Experimenter 1 then highlighting where the food was actually hidden.

### ***Study 2: Structural brain development and executive function in macaques exposed to early psychosocial deprivation: Longitudinal effects across adolescence into adulthood***

In Chapter 4, work that will be included in a paper about the longitudinal effects of early psychosocial deprivation on structural brain development implicated in macaque executive function is presented. Anatomical and diffusion MRI/DTI are utilized here to investigate development in structural connectivity (i.e. white matter microstructure) between brain regions involved in executive function circuitry, as well as grey matter thickness in PFC. MRI data were acquired at the same two time-points as the ‘A not B’ task was conducted (presented in Chapter 3), and therefore MRI and behavioural measures could be compared across adolescence and adulthood.



It was ***hypothesized*** that: ***i***) cortical thickness in PFC regions (vIPFC and dIPFC) would decrease over time, but would remain greater in the peer-reared versus mother-reared group; ***ii***) integrity in fronto-parietal and fronto-striatal white matter tracts would increase over time, but would be lower in in the peer-reared versus mother-reared group; ***iii***) EF measures would be related to cortical thickness in dIPFC and vIPFC and white matter integrity in fronto-parietal and fronto-striatal tracts, with better EF linked to thinner cortex and higher integrity, respectively; ***iv***) working memory and response inhibition would be related to both overlapping and distinct patterns of structural connectivity and cortical thickness in these different regions and circuitry; and ***v***) cortical thickness and white matter integrity would modulate the relationship between psychosocial deprivation and EF across time, with fronto-striatal tracts having greater effects in adulthood compared to adolescence.



**Figure 7.** Example of structural, and diffusion MRI images from a macaque monkey. The first two images are examples of different structural scans (T1, T2); the third is based on a diffusion MRI scan and shows a fractional anisotropy (FA) color map displaying the diffusivity vector V1 (principal direction vector) for each voxel (red represents left-right oriented fibers; blue represents dorsal-ventral oriented fibers; green represents anterior-posterior oriented fibers); and the fourth image depicts a close-up view of the FA map.

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## **CHAPTER 2.**

### **Wider project methodology**

## Project description

The work presented in this thesis is part of a wider project investigating the longitudinal effects of early psychosocial deprivation on neurocognitive development in rhesus macaques from pre-adolescence to adulthood. This project aims to elucidate the mechanisms linking early psychosocial deprivation to specific poor outcomes such as risk for anxiety and symptoms of ADHD, with a focus on self-regulatory processes (e.g. emotion regulation and executive function). To achieve these aims, the project is utilizing a macaque model of early psychosocial deprivation (i.e. peer-rearing). A number of different techniques are being used to assess behavioural and brain development at three-time points corresponding to late childhood, adolescence, and early adulthood, including naturalistic behavioural observation, standardized behavioural assessments, magnetic resonance imaging (MRI; anatomical, diffusion, and resting-state functional), and genetic and hormonal measures.

## Subjects

The sample is composed of 21 Rhesus macaque monkeys (*Macaca mulatta*). As infants, half of these animals were reared by their mother (n = 11; 'mother-reared') and half were reared in a nursery of peers (n = 10, 'peer-reared'); i.e. apart from their mothers and other adults from birth, raised by human caregivers. As such, the peer-reared group were deprived of typical early psychosocial experiences, which, like in humans, is comprised predominantly of mother-infant interactions in macaques (Ferrari et al., 2009; Dario Maestriperi et al., 2009). This sample is unique in Europe, and offers an extremely exciting opportunity to look at the effects of early social deprivation in a very well-controlled manner. See Shannon et al. (1998) for more information on the peer-rearing protocol.

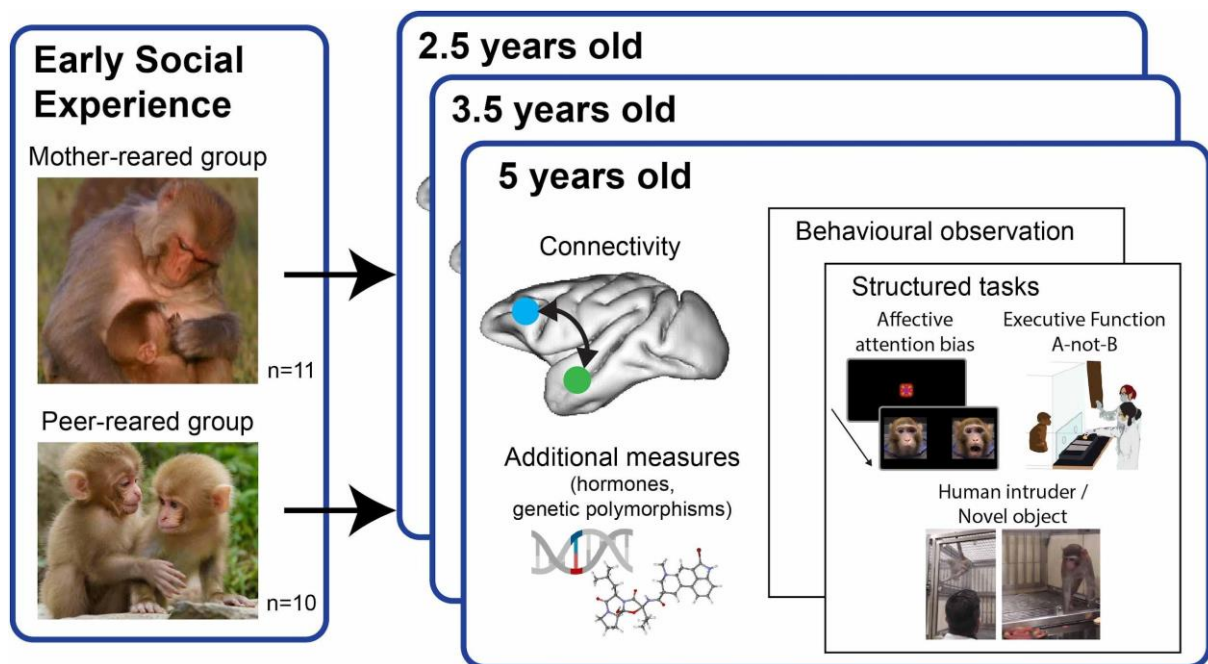
As part of the wider project, assessments were made longitudinally at 2.5, 3.5, and 5 years, corresponding approximately to late childhood, adolescence, and early adulthood in macaques (Figure 1). We assessed the animals at these ages because they represent key transition points in development when many significant changes related to self-regulation occur. All subjects were housed in a single colony at the Rousset Primatological Station, CNRS, in semi-free ranging conditions with indoor and outdoor enclosures. Groups of 5-6 animals

were transferred to the Institut des Sciences Cognitives – Marc Jeannerod (ISC-MJ) in Bron for assessment each year for a number of weeks. At the ISC-MJ, subjects were housed together. All groups contain a balanced mix of mother-reared and peer-reared animals, with groups housed in an indoor enclosure. This enclosure was enriched to allow for meaningful activities and expression of the animals' full behavioural repertoire. MRI assessments were conducted a minimum of two weeks after this relocation. All subjects returned to the Rousset station after data collection, and all animals were kept alive at the end of the study. All housing and procedures conformed to current guidelines concerning the care and use of laboratory animals (European Community Council Directive No. 86-609), and were approved by our local ethics board, Comité d'Éthique Lyonnais pour les Neurosciences Expérimentales (CELYNE) C2EA #42 (03.10.18), and the French Ministry of Research (10.10.18); project reference APAFIS#15091\_2018071014483295\_v2. All reporting here conforms to the recommendations in the ARRIVE Guidelines for Reporting Animal Research.

All subjects were born and raised at the *Laboratory of Comparative Ethology at the National Institutes of Health, US*. At eight months postpartum, mother-reared and peer-reared subjects were placed into a single social group. Rearing procedures were approved by the NICHD and the University of Maryland Animal Care and Use Committee, and adhered to the NIH Guide for the Care and Use of Laboratory Animals. Animals were relocated to the *Rousset Primatological Station, CNRS, France* at two years of age. Although this kind of manipulation of monkeys' early social experience is being widely prohibited in future research with new infant samples, it was decided that in this case, further study of this particular sample of juvenile animals was the most ethical course of action. Due to the closure of the centre in the US where subjects were born and lived for the first two years of life, it was agreed that the ISC-MJ would receive these animals rather than allow them to be euthanized for research where effects of their early social experiences would not be considered; and consequently, failing to maximize the scientific benefit that could be derived from this existing sample. Every effort has been made to ensure that these animals now live in the most enriching environment possible, including their social environment, and tasks included in the project were designed to be as noninvasive as possible.



## Project design



**Figure 1.** *Project design.* 21 Rhesus macaque monkeys (*Macaca mulatta*) were assessed at three time-points (2.5, 3.5, and 5 years) corresponding to late childhood, adolescence, and early adulthood. As infants, half of these animals were exposed to early psychosocial deprivation (i.e. rearing in a nursery of peers by human caregivers) and a half were not (i.e. reared by their biological mothers). At each time point, behavioural and neurobiological data were collected.

### ***Behavioural Assessments***

Behaviour in the two rearing groups was observed in their everyday social environment over a number of weeks in order to collect data concerning anxiety, social competence, and other relevant behaviours linked to poor outcomes often seen in the context of early psychosocial deprivation (e.g. ‘hyperactivity’). Additionally, the subjects were temporarily separated into a designated area of the home enclosure for several structured behavioural tasks. These tasks were designed to assess the subjects’ responses to affective and potentially threatening stimuli (e.g. an unknown human), and thus differences in emotional reactivity and regulation, as well as executive function. The project design is illustrated in Figure 1.

### **Behavioural group observation**

At each of the three project time-points, animals were video recorded (50fps) in their home enclosure (i.e. in the social group) on two days per week (morning and afternoon) for a three-week period (20 minutes per recording). This was for a total of 240 minutes per group.

Two cameras were placed in the room in order to capture a view of the whole enclosure, and recordings from these cameras were synchronized afterwards.

For each animal (i.e. the ‘focal animal’), the last 10 minutes of each video were manually coded, with the first 10 minutes constituting a period of habituation to the cameras. A second-by-second coding scheme based on those used in previous studies was used to identify a number of social and non-social behaviours of interest (Kaburu et al., 2016; Maestriperi, 2010; Pomerantz et al., 2012). A random 15% of videos were coded by a second researcher at the first time-point to establish reliability. Reliability scores obtained between coders were very strong (i.e. all  $\kappa > 0.93$ ). This included coding of anxiety-like behaviour (more details and related results are presented in Appendix A).

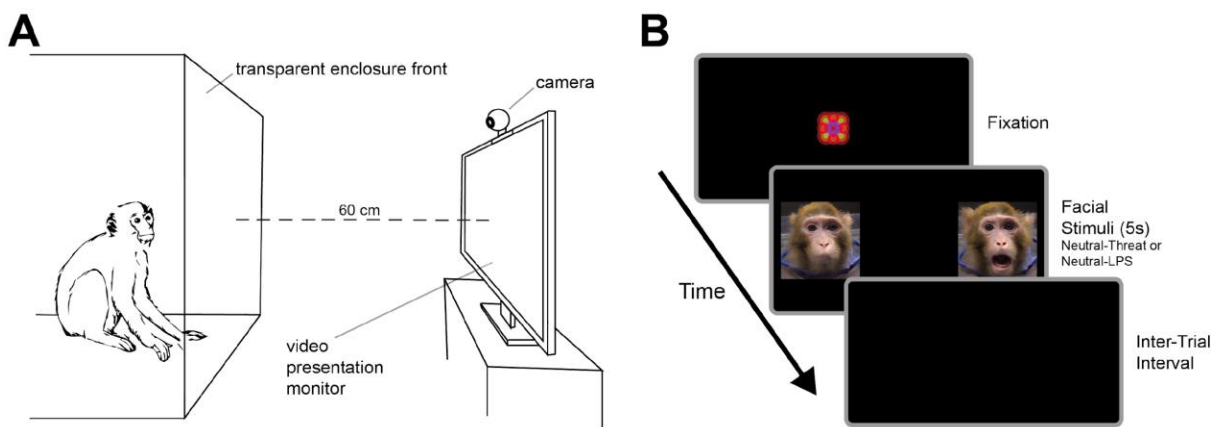
### **Affect-biased attention**

At the first time-point (2.5 years), animals were presented with pairs of affective and neutral facial gestures in order to assess attention biases to threat and reward. Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; an 87 × 100 × 120cm enclosure with a clear panelled front. Before commencing the task, a widescreen computer monitor (35 × 61cm; 2560 × 1440 resolution) was placed 60cm from the front of the enclosure, and animals were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure and presentation of non-social video stimuli before the day of assessment. Animals were recorded during the task using a webcam (30fps) placed on the top-centre of the monitor.

Animals were presented with pairs of neutral-affective gesture stimuli comprising two conditions: i) Neutral-Threat (five trials per subject); and ii) Neutral-LPS (five trials per subject), i.e. the positive or reward condition. Video pairs were presented for 5s per trial, with condition order and position (left or right) of neutral-affective gesture videos counterbalanced across subjects. Before the stimuli appeared, a moving geometric pattern accompanied by a non-social sound was presented in the centre of the screen to attract the subject’s attention, with stimuli presentation then triggered by an experimenter watching the animal live on a separate monitor (not in view of the subject). Additionally, a calibration procedure was conducted before presentation of experimental stimuli, whereby images of objects (e.g. ball, toy car)

were presented on the right, centre, and left of the screen. Each image was jittered up and down slightly to attract attention and was accompanied by a non-social sound. Psychopy v1.90.249 was used for stimulus (calibration and experimental) presentation, with video recording onset and offset automatically triggered at the start and end of each presentation. This sequence and the experimental set-up is illustrated in Figure 2.

Subjects' gaze (left, right, other, offscreen) was manually coded offline, frame-by-frame, by a researcher blind to the condition being presented and the position of the neutral-gesture stimuli. A random 15% of videos were coded by a second researcher to establish reliability, with very good reliability scores obtained (all  $\kappa > 0.84$ ). More details and related results are presented in Appendix A.



**Figure 2.** *Task set up and procedure.* A) Schematic illustration of the gaze bias task set-up; B) Illustration of a trial in the gaze bias task. An experimenter triggered the appearance of fixation and facial stimuli screens when the subject looked towards the monitor.

### **Threat Sensitivity**

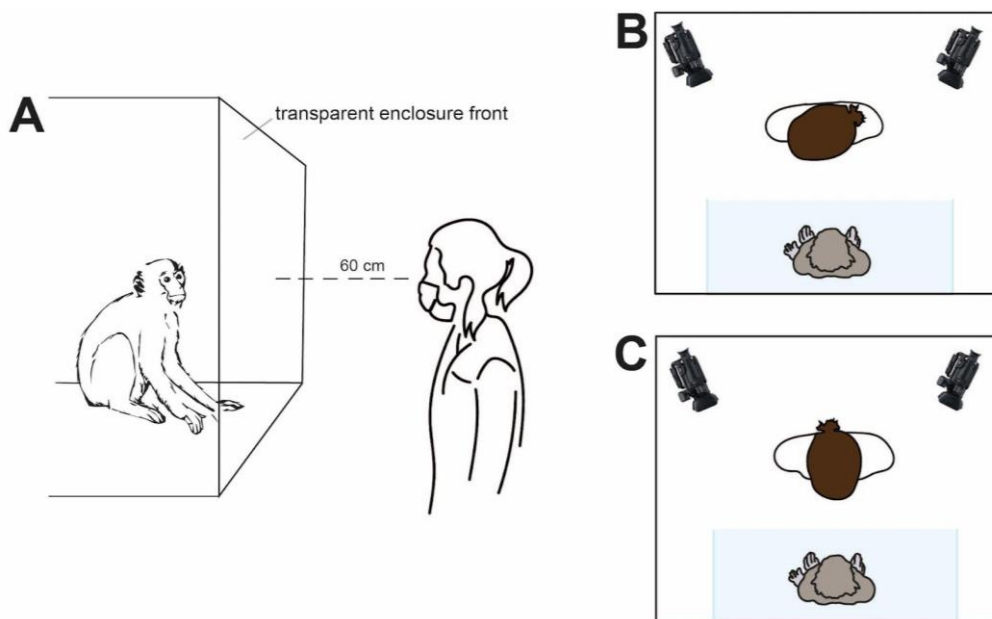
At all three project time-points, subjects' responses to novel social and non-social stimuli differing in threat level were observed.

#### ***Human Intruder (social task):***

A version of the human intruder paradigm (Kalin & Shelton, 1989) was used to assess subjects' affective reactivity to potential social threat; an unfamiliar human (i.e. the 'intruder'). Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; an 87 × 100 × 120cm enclosure with a clear panelled front. Animals

were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure before the day of assessment. Animals were recorded during the task using two cameras (50fps), which were then synchronized offline.

The task comprised four conditions differing in levels of threat to macaque monkeys: i) 'alone', where no intruder was present in the room; ii) 'profile', where the intruder entered the room and stood with their head turned away from the subject to avoid eye contact (low threat); iii) 'alone', where again, no intruder was present in the room; and iv) 'stare', where the intruder entered the room and stood with their head facing forward and making eye contact with the subject (high threat). In the profile and stare conditions, the intruder stood 1m from the front of the testing enclosure. Each condition lasted 2 minutes, and no other experimenter was in the room during the task. The task set-up is illustrated in Figure 3.



**Figure 3.** Schematic illustration of the human intruder task set-up. A) Task setting; B) Low threat 'profile' condition; C) High threat 'stare' condition.

Behaviours of interest such as freezing, aggressive gestures, and affiliative gestures in the different conditions were scored second-by-second from the videos by trained coders. One experimenter coded all of the videos,

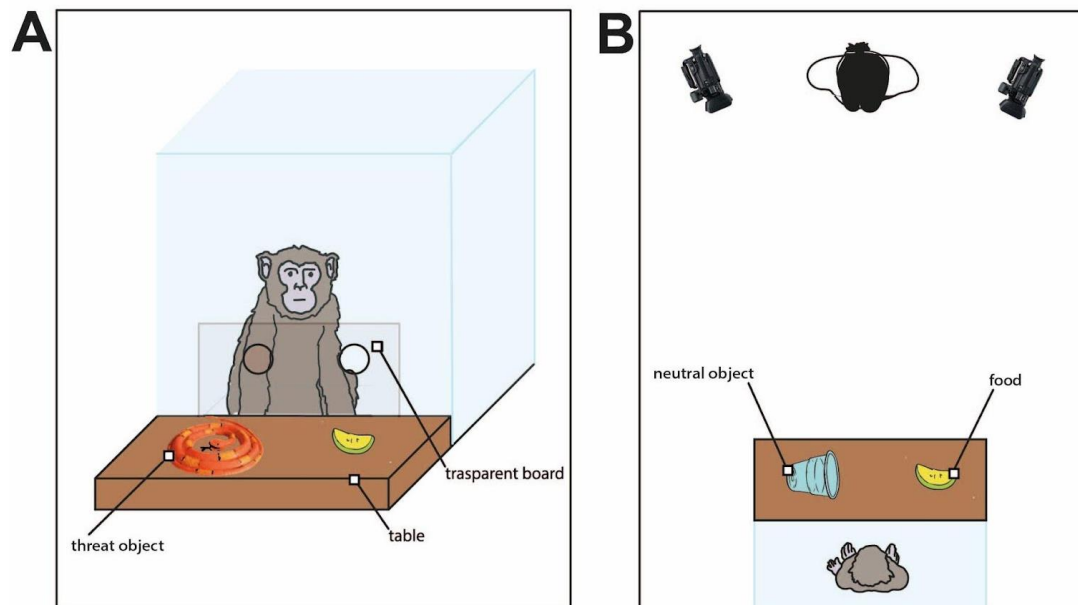
with a second experimenter coding a random 15% at the first time-point to establish reliability (all  $\kappa > 0.9$ ). More details and related results are presented in Appendix A.

***Novel Object (non-social task):***

A version of this paradigm (Howell et al., 2014) was used to assess subjects' affective reactivity to potential non-social threat; a neutral object (e.g. a cup) or a threatening object (e.g. a plastic snake). Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; an 87 × 100 × 120cm enclosure with a clear panelled front. Animals were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure before the day of assessment. Animals were recorded during the task using two cameras (50fps), which were then synchronized offline.

There were two holes in the transparent front panel of the testing area that allowed subjects to access objects on a table outside the enclosure; though these holes were not large enough for animals to bring neutral and threatening objects inside the testing area. One experimenter was present during the task. The task comprised three conditions differing in levels of threat: i) 'food alone', where a piece of food was placed on one side of the table (baseline); ii) 'neutral', where a neutral object was placed on the table on the opposite side to a piece of food; and iii) 'threat', where a threatening object was placed on the table on the opposite side to a piece of food. The position of both the food and the objects was counterbalanced for each subject. The first condition was always 'food alone', while the order of 'neutral' and 'threat' conditions was counterbalanced across subjects. Each condition lasted 2 minutes. At the beginning of each of the three conditions, the experimenter moved forward to the table in front of the testing area, always looking down, and placed the food or the food and object (simultaneously) on the table. From that moment the 2 minutes for that condition began, and the experimenter stepped back and

remained in a still position with their head down and arms behind their back. The task set-up is illustrated in Figure 4.



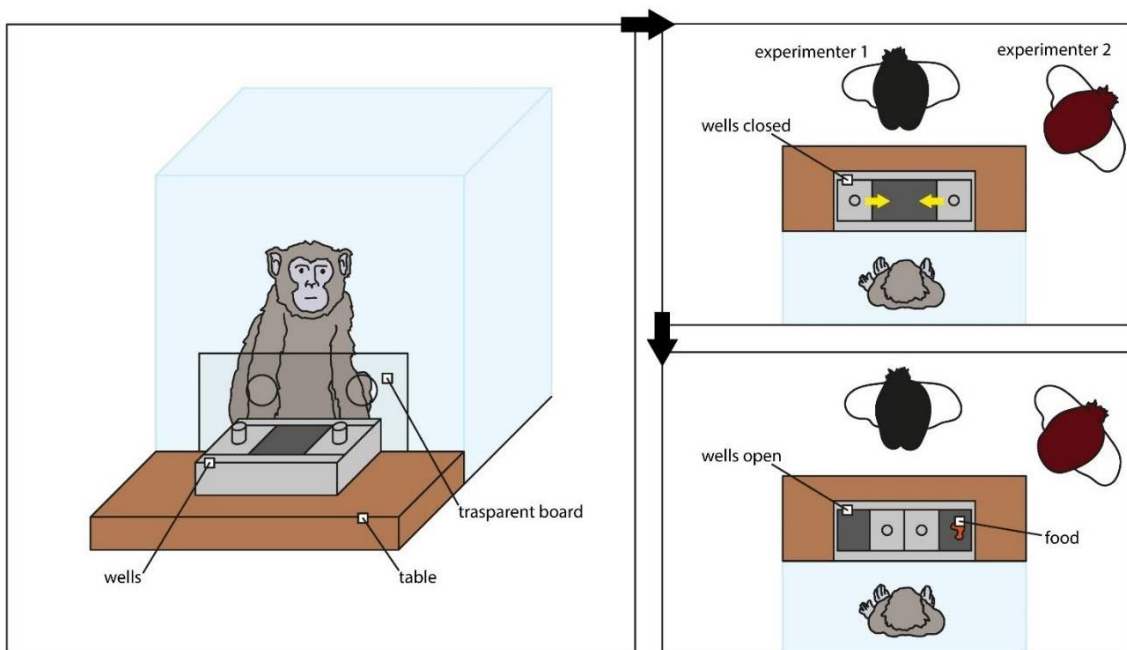
**Figure 4.** Schematic illustration of the novel object task set-up. A) Setting example for the threat condition; B) Setting example for the neutral condition.

### **Executive Function**

At time-points two and three (3.5 and 5 years), an 'A not B' task adapted from the human developmental literature (Diamond & Goldman-Rakic, 1989; Holmboe et al., 2008) was used to assess EF. Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; an 87 × 100 × 120cm enclosure with a clear panelled front. Animals were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure before the day of assessment, as well as the equipment used in the task. Choice in each trial was scored live, with animals also recorded during the task using one camera in order to code other behaviours offline (50fps).

There were two holes in the transparent front panel of the testing area that allowed subjects to access objects on a table outside the enclosure. A box with two wells and sliding doors was placed on the table. Two experimenters were present during the task. The task set-up can be seen in Figure 5.

In each trial, an experimenter presented a piece of food to the subject, and then placed it in one of the wells and covered both wells with the sliding doors. The trial only proceeded if the subject looked at the food when it was presented and when it was hidden. After a delay period, during which the subject's physical and visual access to the wells was blocked, the subject was allowed to reach for the wells. If the subject reached for the correct well, they were allowed to eat the food, otherwise, the correct well was opened to show them the food. If the subject touched both wells, didn't respond, or the response was unclear, the trial was repeated. The location of the food was changed after the subject reached for the correct well on two consecutive trials. The subjects completed two testing sessions at each assessment time-point, with a maximum of 25 trials per session (50 trials total per time-point). The delay period was adjusted based on the subject's performance. More details and results are presented in Chapters 3 and 4.

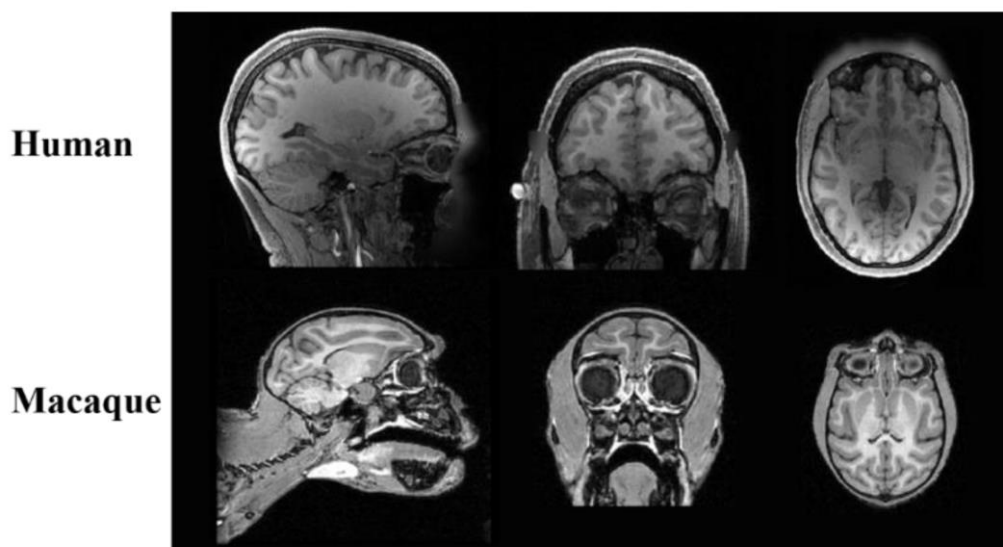


**Figure 5.** *Task set-up.* A frontal view of the testing enclosure is illustrated on the left. Two views from above are illustrated on the right: *upper right*, the wells are closed with the yellow arrows indicating a sliding mechanism; *upper left*, the wells are open and a piece of food is placed in one of them.

### ***Magnetic Resonance Imaging (MRI)***

To investigate changes in brain morphology and both structural and functional connectivity, magnetic resonance imaging (MRI) data were collected at each project time point (2.5, 3.5, and 5 years) using a 3T Siemens Prisma MR scanner. The subjects were

separated from their social group for a total of approximately 5 hours to undergo the scanning process. This time period included one hour for preparation, including anaesthesia induction, intubation, and positioning in the scanner, three hours of active scanning, and one hour of post-anaesthesia recovery. During the scan, the subjects were positioned in a supine position and were anaesthetized with isoflurane (1.5%/2% isoflurane via intubation). A stereotaxic frame was employed to secure the head and prevent movement in order to mitigate motion artefacts. A Vitamin E capsule was placed on the right temple to serve as a marker for the right brain hemisphere. Alphaxalone was administered for anaesthesia induction, and NaCl was administered intravenously for hydration during the scan. We used local anaesthetic cream (Anesederm) externally on the ears prior to the installation of the subject in the stereotaxic frame. The subjects were also placed under an MRI-compatible heating blanket to maintain body temperature. Physiological measures such as heart rate, temperature, and blood oxygenation were continuously monitored and maintained in accordance with veterinary protocols throughout the scan. Upon completion of the scan and full recovery from anaesthesia, the subjects were returned to their social group.

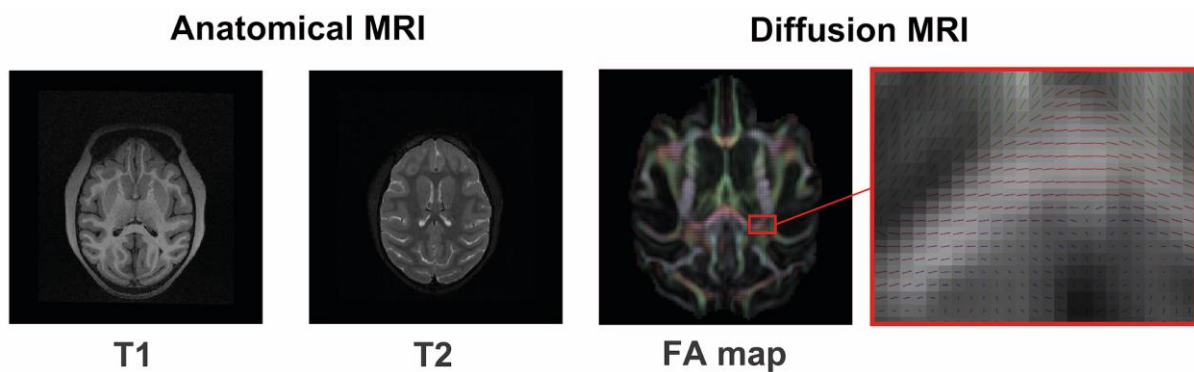


**Figure 6.** Example of an anatomical T1 scan in axial, coronal, and sagittal views in both humans and macaques. (Figure from Wang et al., 2022)

Three types of scan were collected: **High resolution anatomical MRI (T1/T2) scans** were obtained in order to look at brain morphology: MPRAGE T1-weighted images, 0.5mm isotropic, a bandwidth of 250Hz, a TR of 3000ms, a TE of 3.62ms, a TI of 1100ms, a flip angle of 8° and 144 cross-sections, and SPACE T2-weighted images with a spatial resolution of



0.5mm isotropic, a bandwidth of 710Hz, a TR of 3000ms, a TE of 366ms, a flip angle of 120° and 144 cross-sections acquired (Figure 7). **High resolution diffusion MRI scans** were acquired to investigate brain microstructure: custom pulse sequence based on a segmented 3-dimensional EPI sampling of Fourier space with the following parameters; diffusion weighted images (b-value of 1000s/mm<sup>2</sup>), 46 directions diffusion gradient encoding with two B<sub>0</sub>, a spatial resolution of 0.8mm isotropic, a bandwidth of 776Hz, a TR of 750 ms, a TE of 71ms, 4 segments, a FOV of 105x125x56mm<sup>3</sup> and an acquisition time of 60 minutes 38 (Tounekti et al., 2018) (Figure 7). **Resting-state functional MRI scans** were obtained to investigate functional brain connectivity: optimized gradient-echo T<sub>2</sub>\*-weighted Echo Planar Imaging (EPI) sequence, in partially parallel acquisition mode with foot-head acceleration direction and an acceleration factor of 2 (Grappa 2). The field of view (FOV) of read-out will be 105mm and that of phase 95mm. The repetition time (TR) were 2000ms and the voxel resolution 1.27x1.27x1.27mm. Molday ION, a contrast agent, were injected intravenously prior to the resting-state functional MRI scans at the quantity of 11mg/kg to enhance the signal-noise ratio and have a better spatial resolution for the analysis. More information about the MRI and related results are presented in Chapter 4, and appendices A, B, and C.



**Figure 7.** Example of structural, and diffusion MRI images from a macaque monkey. The first two images are examples of different structural scans (T1, T2); the third is based on a diffusion MRI scan and shows a fractional anisotropy (FA) color map displaying the diffusivity vector V<sub>1</sub> (principal direction vector) for each voxel (red represents left-right oriented fibers; blue represents dorsal-ventral oriented fibers; green represents anterior-posterior oriented fibers); and the fourth image depicts a close-up view of the FA map.

### **Endocrine and genetic assessments**

At each project time-point, blood and hair samples were collected after anaesthesia induction for the MRI acquisition. These were collected so that relevant endocrine and genetic

measures could also be considered (e.g. genetic polymorphisms of the serotonin transporter gene and hair cortisol levels, both of which have been linked to emotion dysregulation). **Blood samples** (4ml/kg) were collected while the animals were sedated, and were then stored in a refrigerator at -80 degrees Celsius prior ready for processing. **Hair samples** were obtained by shaving the subject's fur with an electric razor from the back of the neck (to the ears) and stored in a refrigerator at -20 degrees Celsius.

## This thesis

The focus of the research presented in this thesis is on the development of executive function across adolescence in rhesus macaques exposed to psychosocial adversity, as well as the structural measures of brain development that may modulate executive function in this context. Executive function is a key predictor of academic, socio-emotional, and occupational success, as well as risk for psychopathology, and is thought to rely on a sensitive period of brain development characterized by maturation of the prefrontal cortex (PFC) and related networks. Main results are presented in two separate studies (**Chapters 3 and 4**).

**Chapter 3** comprises a submitted paper (Massera et al., *in press*) in which the longitudinal effects of early psychosocial deprivation on executive function in rhesus macaques is investigated. The study utilized the 'A-not-B' task described above to assess general executive function at 3.5 and 5 years, with the fitting of a computational model of decision-making also used to functionally decompose the precise EF mechanisms (i.e. working memory and inhibitory control) that may underlie task performance. In **Chapter 4**, the longitudinal relationship between these executive function measures and structural measures of brain development in the PFC and in frontoparietal and frontostriatal white matter tracts (i.e. crucial circuitry implicated in executive function) using anatomical and diffusion MRI.

Additional findings related to emotion regulation and anxiety in the context of psychosocial deprivation are presented in **Appendix A**, including results showing a modulatory role of alterations in structural brain connectivity. This includes a published paper based on behaviour at the first time-point (Rayson et al., 2021), and preliminary results involving diffusion MRI. In **Appendix B**, supplementary analyses on MRI measures including all three time-points are presented. **Appendix C** contains a number of posters illustrating some

preliminary resting-state fMRI results concerning amygdala and pulvinar connectivity with cortex, as well as behavioural results from Chapter 3.

Note, the MRI portion of this work was completed in collaboration with the research teams of Bassem Hiba and Suliann Ben Hamed. All work involving anatomical and diffusion MRI was led by Bassem Hiba; Hind Errame, with the help of Nathalie Richard and Yann Bihan-Poudec, preprocessed all the data and performed some of the analyses presented in **Chapter 4** under the supervision of Dr Hiba. All work involving resting-state fMRI was led by Dr Ben Hamed; Simon Clavengier and Mathilda Froesel preprocessed and analysed the data. Mathilda Froesel and Maeva Gacoin were involved in all MRI data acquisition, under the supervision of Dr Ben Hamed.

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## **CHAPTER 3.**

### **Longitudinal effects of early psychosocial deprivation on macaque executive function: evidence from computational modelling**

# Longitudinal effects of early psychosocial deprivation on macaque executive function: Evidence from computational modelling

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## Abstract

Executive function (EF) describes a group of cognitive processes underlying the organization and control of goal-directed behaviour. Environmental experience appears to play a crucial role in EF development, with early psychosocial deprivation often linked to EF impairment. However, many questions remain concerning the developmental trajectories of EF after exposure to deprivation, especially concerning specific mechanisms. Accordingly, using an 'A-not B' paradigm and a macaque model of early psychosocial deprivation, we investigated how early deprivation influences EF development longitudinally from adolescence into early adulthood. The contribution of working memory and inhibitory control mechanisms were examined specifically via the fitting of a computational model of decision making to the choice behaviour of each individual. As predicted, peer-reared animals (i.e. those exposed to early psychosocial deprivation) performed worse than mother-reared animals across time, with the fitted model parameters yielding novel insights into the functional decomposition of group-level EF differences underlying task performance. Results indicated differential trajectories of inhibitory control and working memory development in the two groups. Such findings not only extend our knowledge of how early deprivation influences EF longitudinally, but also provide support for the utility of computational modelling to elucidate specific mechanisms linking early psychosocial deprivation to long-term poor outcomes.



## Introduction

Executive function (EF) refers to a group of cognitive processes that underlie the organization and control of goal-directed behaviour. One prominent theory defines EF as a construct comprising a number of interrelated, but distinct, components (Friedman & Miyake, 2017). These include working memory, inhibitory control, and cognitive flexibility, with some common underlying processes connecting them (Miyake et al., 2000). EF develops rapidly between birth and two years of age, with steady development then continuing into early adulthood (Ferguson et al., 2021; Fiske & Holmboe, 2019). Such protracted development suggests continued plasticity of EF, as does the extended developmental trajectory of neural networks supporting EF (e.g. fronto-parietal network) (Fiske & Holmboe, 2019; MacNeill et al., 2018; Tervo-Clemmens et al., 2022). Critically, individual differences in childhood EF are related to later social competence, academic performance, and occupational functioning (Blair & Razza, 2007; Miller et al., 2011; Spiegel et al., 2021), as well as risk for interpersonal problems and risky behaviour during adolescence and adulthood (Fairchild et al., 2009; Gustavson et al., 2017). EF deficits are also characteristic of a number of neurodevelopmental disorders, including attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) (Bloemen et al., 2018; Demetriou et al., 2017; Willcutt et al., 2005). However, despite the clear importance of EF for healthy development (Snyder et al., 2015), many questions remain concerning the factors underlying different developmental trajectories of EF, and thus the individuals most at risk for poor outcomes.

Evidence is growing for early environmental experience playing an important role in EF development. Indeed, early social adversity has been consistently linked to EF impairments in childhood (e.g. (Demir-Lira et al., 2016; Gunnar & Reid, 2019; Lund et al., 2020)), with early psychosocial deprivation, a specific form of early social adversity involving removal of an infant from their primary caregivers, having a particularly profound effect on EF components such as working memory and inhibitory control (Bos et al., 2009; C. E. Hostinar et al., 2012; Johnson et al., 2021; Wade et al., 2019). Relevantly, increased risk for ADHD is also associated with early psychosocial deprivation (Golm et al., 2021; Jennifer Martin McDermott et al., 2013), as is risk for symptoms such as disinhibited social engagement and repetitive and stereotyped behaviour (Sonuga-Barke et al., 2017). A lack of complexity and socio-cognitive stimulation in the early social environment, along with increased levels of stress, could explain

why early psychosocial deprivation has such a significant impact on EF. For example, this can lead to excessive and less selective pruning of synapses in the cortex, including prefrontal regions implicated in higher cognitive abilities (Vogel et al., 2021). In support of this, deprivation has regularly been associated with a generalized reduction of grey matter in prefrontal, parietal, and temporal cortical regions (McLaughlin et al., 2019).

The few longitudinal studies conducted on this topic suggest that poor EF associated with early psychosocial deprivation in early life can persist into adolescence and adulthood (Golm et al., 2021; Lund et al., 2022; McGinnis et al., 2022; Wade et al., 2019), but as most studies only evaluated EF at one time-point (Bos et al., 2009; Camelia E. Hostinar et al., 2012; Jennifer M. McDermott et al., 2012; Pollak et al., 2010), many questions about long-lasting effects on EF and the neural mechanisms underlying this relationship across time remain unanswered. Longitudinal research is now essential for enhancing our understanding of how various aspects of cognition develop in terms of both typical and atypical trajectories. The tracking of EF across adolescence into adulthood will be a particularly key period of transition for future examination in studies of psychosocial deprivation. Adolescence is a period of heightened brain plasticity defined by significant development of prefrontal cortex (Laube et al., 2020; Paquola et al., 2019), as well as important refinements of EF (Tervo-Clemmens et al., 2022). As such, adolescence may be a particularly useful target for interventions aimed at preventing or ameliorating adverse effects of early deprivation on cognitive development.

The use of a nonhuman primate (NHP) model such as rhesus macaques (*Macaca mulatta*) could be very helpful to address outstanding questions about the effects of early psychosocial deprivation on EF across development. Macaque monkeys are one of the closest species to humans in terms of genetics, physiology, and behaviour, and have an extended period of development comprising distinct infant, juvenile (pre-adolescent and adolescent), and adult stages. Like humans, their early social environment is also comprised predominantly of mother-infant interactions. Notably, the use of a macaque model can help address some limitations defining developmental studies with humans: e.g. lack of control over the early environment, very long developmental time-frames, and difficulty in tracking neural mechanisms underlying development. Although limited, research focused on EF development in macaques suggests that it parallels that in humans (Rathke & Fischer, 2020; Verrico et al., 2011; Watzek et al., 2019; Weed et al., 2008), and in adult macaques, EF relies on the same

cortical networks (Mansouri et al., 2020; Stoet & Snyder, 2009). Limited research focused on early psychosocial deprivation effects on cognition in infant macaques have produced mixed findings (e.g. (Murphy & Dettmer, 2020; Sánchez et al., 1998)), with research comparing deprived versus non-deprived animals especially rare. Discrepancies in findings concerning effects of early psychosocial deprivation on cognitive ability may stem from differences in age at assessment and use of different measures at different time-points, and no studies thus far have focused on EF specifically.

A classic paradigm used to investigate EF in human infants and young children is the 'A-not-B' task (Cuevas & Bell, 2010; Espy et al., 1999; Piaget, 1954), which is thought to measure two EF components: inhibitory control and working memory (Cuevas & Bell, 2014; Diamond & Goldman-Rakic, 1989; Holmboe et al., 2018). Modified versions of the 'A-not-B' task have also been used to investigate EF in trained adult macaques. Macaque behaviour during the task is comparable to human performance (Caselli & Chelazzi, 2011; Diamond & Goldman-Rakic, 1989). No previous research has used an 'A-not-B' task to look at macaque EF development or effects of early psychosocial deprivation, though a version such as that used with human infants could offer a valuable way to test EF without removal of the animals from their home enclosure and extensive training. A data collection approach that requires these two elements is starting to be adopted by other researchers (Dettmer et al., 2015; Murphy & Dettmer, 2020), who argue that it enables a more direct comparison of cognitive development in macaques exposed to early psychosocial deprivation versus non-exposed macaques.

Although the 'A-not-B' task is assumed to involve both working memory and inhibitory control mechanisms, it has been recently argued that these components are difficult to disentangle using classic measures of response accuracy according to condition (Hendry et al., 2021; Holmboe et al., 2021). Developing tasks that do not rely on instruction in order to assess specific EF components in infancy and early childhood (Hendry et al., 2021; Holmboe et al., 2021) is very challenging, but another option to help isolate mechanisms underlying behaviour in the 'A-not-B' task is to use computational modelling. Specifically, using a computational model of decision making to functionally decompose choice behaviour into working memory and inhibitory control mechanisms would enable both examination of these specific EF components, as well as a way to evaluate how well previously utilized 'A-not-B' performance measures actually assess these components.

Accordingly, the current study was designed to investigate the longitudinal effects of early psychosocial deprivation on EF in rhesus macaques using a computational modelling approach. We assessed EF in a rare sample of macaques comprised of two groups that differed in exposure to early psychosocial deprivation; one mother-reared and one peer-reared (i.e. exposed to early psychosocial deprivation; separated from their mothers and other adults at birth and raised in a nursery of peers by human caretakers); at two time-points corresponding to adolescence (3.5 years) and early adulthood (5 years). We used a version of the 'A-not-B' paradigm often used with human infants (Holmboe et al., 2018), with animals completing the task in a section of their home enclosure. The choice behaviour of each animal at each time-point was fit with a stochastic computational model of decision-making based on a weighted sum of exponentially decaying working memory and choice history influences. Choice history correspond to inhibitory control, the tendency to suppress previous responses or to repeat them. We then compared the fitted model parameters between groups and across time, as well as to previously utilized performance measures (Holmboe et al., 2008, 2018). We predicted that peer-reared animals would perform worse than mother-reared animals on the task at both time-points, and that both working memory and inhibitory control would be poorer in the peer-reared group.

## Methods

### *Subjects*

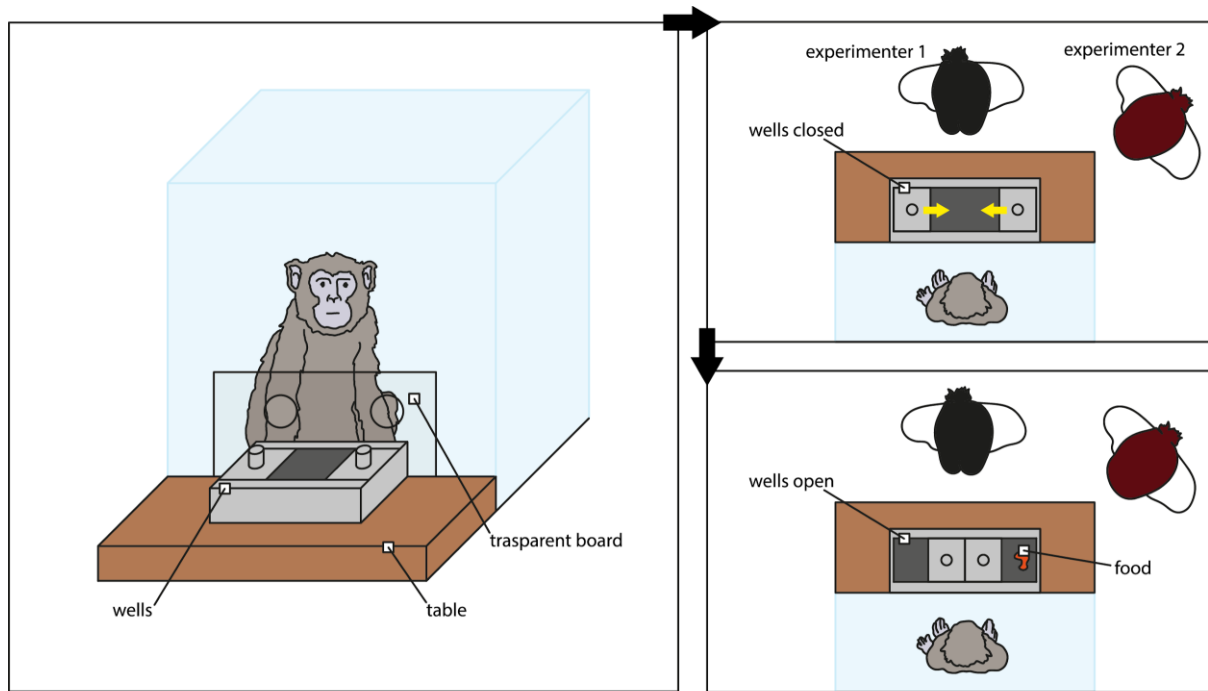
The sample consisted of 21 Rhesus macaque monkeys (*Macaca mulatta*), 11 mother-reared (five female) and 10 peer-reared (six female). Subjects were aged around 3.5 years at the first assessment time-point (mother-reared; M = 1368 days, SD = 104 days: peer-reared; M = 1363 days, SD = 101 days) and 5 years at the second assessment time-point (mother-reared; M = 1806 days, SD = 100 days: peer-reared; M = 1809 days, SD = 95 days). Subjects were housed at the *Institut des Sciences Cognitives Marc Jeannerod*, CNRS, during the assessment period in mixed mother- and peer-reared social groups of 5–6 animals (see SI for rearing protocol). Although new instances of maternal separation in monkeys' for research is largely prohibited, it was decided that further study of this particular sample of juvenile animals was the most ethical course of action. Due to the closure of the center in the US where

animals were born and lived for the first two years of life, it was agreed that our team at the ISC-MJ would receive these animals rather than allow them to be euthanized for medical research whereby effects of their early social experiences would not be considered; and consequently, would fail therefore to maximize the scientific benefit that could be derived from this existing sample. Every effort has been made to ensure that these animals now live in the most enriching environment possible, including their social environment, and the tasks included in the current study was designed to be as noninvasive as possible. All housing and procedures conformed to current guidelines concerning the care and use of laboratory animals (European Community Council Directive No. 86-609), and were approved by our local ethics board, Comité d’Ethique Lyonnais pour les Neurosciences Expérimentales (CELYNE) C2EA #42 (03.10.18), and the French Ministry of Research (10.10.18); project reference APAFIS#15091\_2018071014483295\_v2. All reporting here conforms to the recommendations in the ARRIVE Guidelines for Reporting Animal Research.

### ***‘A-not-B’ task set-up and procedure***

Each subject was temporarily separated into the testing area, which was a section of the home enclosure; an 87 × 100 × 120cm area with a clear-panelled front. All equipment required for the task was installed before separating the subject. Note, all animals had already been well familiarized with this process of separation into the testing area and with the task equipment.

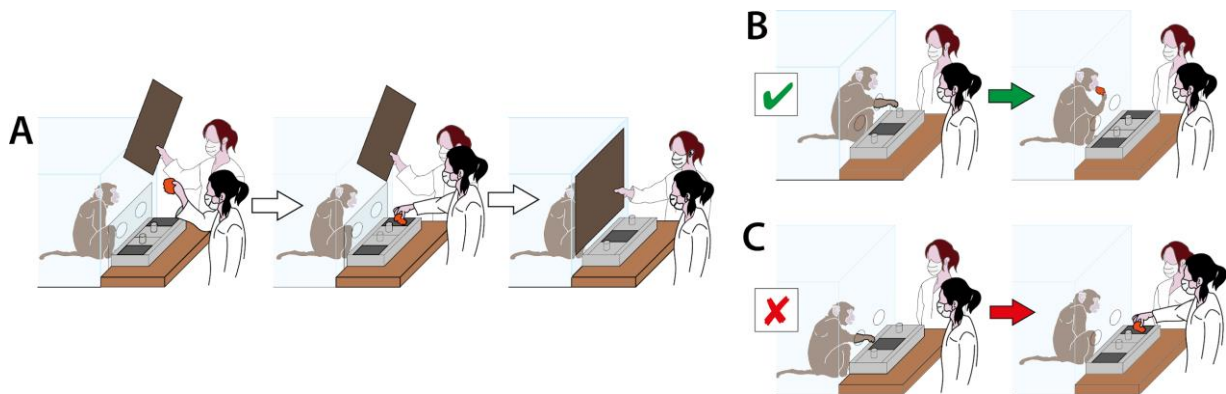
The task set-up included two holes in the clear-panelled front of the testing area which enabled the subject to reach objects placed on a table outside the enclosure (Figure 1). A transparent board was used to block these holes at times when the subject was not allowed to reach (i.e. during the hiding and delay portions of the task; see Procedure section). A box with two wells and two sliding doors to cover the wells was positioned centrally on the table in front of the two holes. The wells were 11.2 cm in diameter and were positioned 18 cm apart. Two experimenters were present for the entire task. Experimenter 1 stood facing the subject, while Experimenter 2 stood on one side of the table, with the side counterbalanced across subjects and sessions.



**Figure 1.** *Task set-up.* A frontal view of the test enclosure is illustrated on the left. Two views from above are illustrated on the right: upper right, the wells are closed with the yellow arrows indicating a sliding mechanism; upper left, the wells are open and a piece of food is placed in one of them.

To begin a trial, Experimenter 1 showed a piece of food to the subject in the centre of their visual field (Figure 2A). Once the subject looked at the food, Experimenter 1 placed the food in one of the wells and closed the two sliding doors to cover both wells. The trial only proceeded if the subject looked at the food when it was presented and when it was hidden. As soon as the wells were covered, a delay period started. During this delay, as well as physical access to the wells being blocked by the transparent board, Experimenter 2 blocked the subject's visual access to the wells with an opaque screen placed between the box and the enclosure front. At the end of the delay, the opaque screen and the transparent board were removed, allowing the subject to reach for the wells. If the subject reached for the correct well, the experimenter allowed the subject to eat the piece of food (Figure 2B). If the subject reached for the incorrect well, the experimenter opened the correct well to show the position of the food to the subject (Figure 2C). If the subject touched both wells, did not respond, or the response was unclear, the trial was repeated. The food was hidden in the same location (left or right well) until the subject reached for the correct well on two consecutive trials. After two consecutive correct trials, Experimenter 1 changed locations and hid the food in the other well (i.e. it was a 'change' trial). After the change trial, the experimenter then repeated this

sequence but on the same side as the preceding change trial. For the first trial of each session, the delay period when visual and physical access to the wells was blocked lasted 2s, and then depending on the subject's performance, it was increased or decreased in subsequent trials. The delay period was decreased by 2s if two consecutive trials were incorrect, and was increased by 1s if two consecutive change trials were correct (Holmboe et al., 2008, 2018). Each subject completed two testing sessions at each assessment time point, with a maximum of 25 trials per session (i.e. 50 trials total per assessment time-point). During each session, Experimenter 1 live-coded correct and incorrect trials, and animals were also video recorded throughout the session with a camera placed to capture a view of the enclosure and Experimenter 1.



**Figure 2. Task procedure.** The series of images illustrates the sequence of a single trial. In the first three images (A) Experimenter 1 shows the food to the subject, places it in the well, and Experimenter 2 blocks the vision of the subject during the delay period. The top right images (B) illustrate a 'correct' choice, with the subject reaching for the well where the food was hidden and then eating the food. The bottom right images (C) illustrate an 'incorrect' choice, with the subject choosing the well containing no food and Experimenter 1 then highlighting where the food was actually hidden.

### ***Control task set-up and procedure***

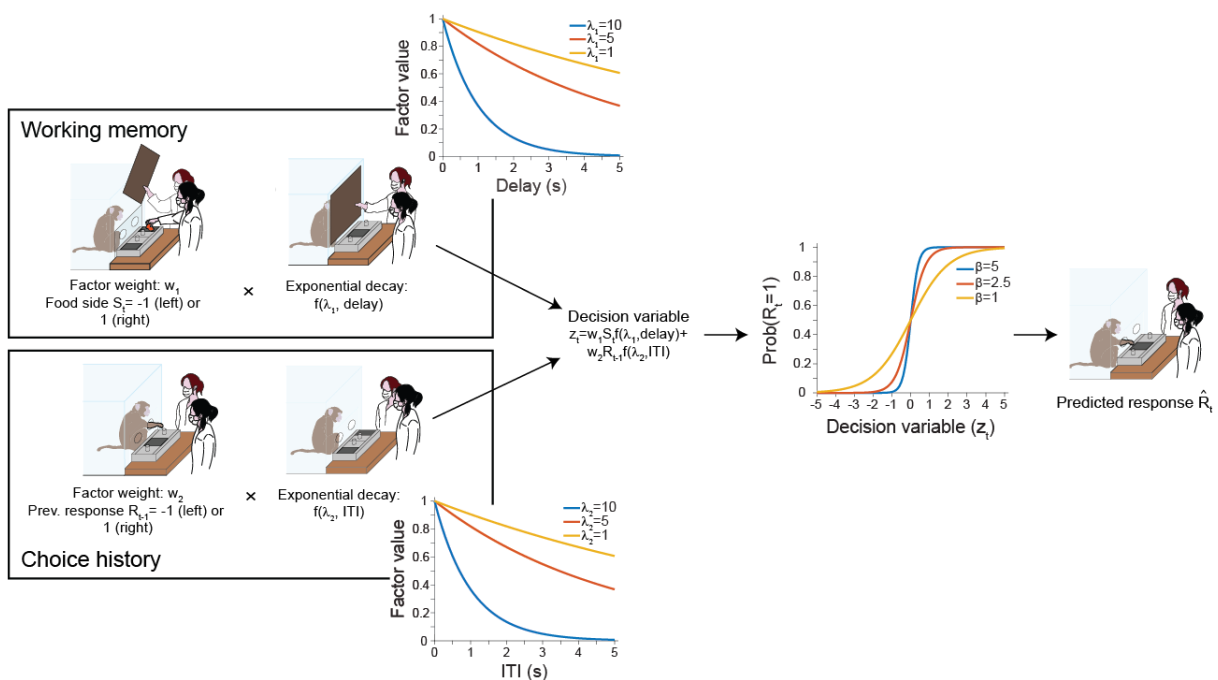
At the second assessment time-point, all subjects also completed a control task to verify that results from the original version of our 'A-not-B' task were not a consequence of the structure of the task. In the original version, the length of the delay period depended on the performance of the subject, with poorly performing subjects not being tested at higher delays. Moreover, if the subjects were always correct, they could have possibly learned the pattern of the hiding locations (e.g. A, A, B, B, B, A, A, B). Therefore, while the task set-up was the same as in the original 'A-not-B' task, the procedure was different. In this new randomized control version of the task, the position of the food hiding location (i.e. left or right well) and

the length of the delay period were pseudo-randomized across trials. The hiding position could not be the same for more than five consecutive trials, and the delay period was a maximum of five seconds. All subjects completed the same number of trials with a specific delay in a specific location (e.g. 3 seconds, right well). Each subject completed two sessions, with a maximum of 24 trials per session (i.e. 48 trials total). With this version of the task, then, all animals were tested equally on all the different possible delays (i.e. from a 0 second delay to a 5 second delay).

### Video coding

A number of parameters were coded offline from the video recordings made of each subject during the testing sessions, including the actual length of delay periods (which may have varied slightly from the intended delay period) in seconds and the inter-trial-interval (ITI) lengths in seconds (see SI).

### Computational model



**Figure 3. Model architecture.** The model included a decaying working memory trace of the food location (top left, the plot shows the influence of decay rate: with higher decay rates, the influence of working memory diminishes faster), and a decaying trace of the previous choice (bottom left, the plot shows the influence of decay rate: with higher decay rates, the influence of the previous choice diminishes faster). The weighted sum of these influences is used to compute the probability of choosing one side or the other using a softmax function (the plot shows the influence of the inverse softmax temperature parameter: at higher values, the decision is more deterministic).



A computational model of decision-making was fitted to the decision behaviour of each subject (chosen out of eleven candidate models based on model comparison; see SI). The model included two influences on the decision to choose the left or right side (Figure 3). The first influence was a decaying working memory trace,  $m$ , of where the food was hidden. We modeled this as an exponential decay function (see Baddeley, 2012 for a discussion of working memory models) according to the delay on trial  $t$ ,  $d_t$ :

$$m_t = w_1 S_t e^{-\lambda_1 d_t}$$

where  $w_1$  is the weight of this factor when the delay is 0,  $S_t$  is the side that food was hidden on in trial  $t$  (left = -1, right = 1), and  $\lambda_1$  is the working memory decay rate. The second influence was that of the previous two choices,  $p$ . We assumed that the strength of this influence would also decrease with time (Bonaiuto et al., 2016), and we therefore also modeled this influence as an exponential decay function according to the inter-trial interval before trial  $t$ ,  $i_t$ :

$$p_t = w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)})$$

where,  $w_2$  is the weight of this factor when the inter-trial interval and delay is 0,  $R_{t-1}$  is the response made on the previous trial (left = -1, right = 1), and  $\lambda_2$  is the decay rate. Positive values of  $w_2$  therefore represent a tendency to repeat the previous choice, whereas negative values represent a tendency to suppress the previous choice, via different degrees of inhibitory control.

The decision variable,  $z$ , was computed as the sum of these two factors,  $m$  and  $p$ , with negative values of representing a tendency to choose the left side, and positive values a tendency to choose the right side. The decision variable was then transformed into the probability of choosing the right side on trial  $t$  using the softmax operator (Sutton, and Barto, 1998):

$$P(R_t = 1) = \frac{1}{1 + e^{-\beta z_t}}$$

The inverse softmax temperature,  $\beta$ , determines the steepness of the softmax function, and thus how sensitive the choice probability is to  $z$ . We refer to this parameter as representing ‘choice stochasticity’, as it captures the balance between exploration and exploitation.

The model was fit separately to each subject's choice behaviour using maximum log-likelihood estimation in Matlab (v R2018a) to find the parameter values that optimize the likelihood that the model would produce the same choices. This process can get stuck in local maxima, a situation in which any small change to the current parameter values decreases the log-likelihood. To avoid this situation, the optimization can be run multiple times, each time with a different initial guess for each parameter value, taking the parameter values with the overall maximum log-likelihood. To ensure that a large portion of the space of possible parameter values was explored, a grid search over all parameter values was used to initialize model parameters before fitting (Lockwood & Klein-Flügge, 2021). The weight of the working memory factor,  $w_1$ , was restricted to the range [0, 1], and the weight of the choice history factor,  $w_2$  was restricted to [-1, 1] in order to detect both a tendency to inhibit or repeat the previous choice reflecting different degrees of inhibitory control. These ranges served to normalize the contributions of each factor to the decision variable. The decay rate parameters,  $\lambda_1$  and  $\lambda_2$ , and the inverse softmax temperature,  $\beta$ , were constrained to be in the range [0,10] to avoid asymptotic values in which further increases in value have no effect on behaviour.

### ***Data analysis***

Before analysis, we checked if any coded behaviours that occurred during either a trial or the ITI were affecting the ability of the model to predict the responses of the subjects. We found that locomotion during trials was the only behaviour negatively impacting the model's prediction accuracy, and therefore we excluded all the trials in which locomotion occurred (see SI). We also removed trials in which the ITI was more than 2.5 standard deviations above the mean, and we excluded subjects with less than 25 remaining trials (one mother-reared subject from both the original task at the first time-point and the randomized control version at the second time-point). We then checked if there was a difference in ITI duration between the two rearing groups, and we found no difference (see SI).

To compare performance on the original 'A-not-B' task between the two rearing groups over time, we computed three measures based on previous literature (e.g. Holmboe et al., 2008, 2018): i) percentage of correct responses (i.e. proportion of correct trials out of all trials completed); ii) cumulative score (the sum of successful change trial delays divided by the number of total trials completed); and iii) maximum delay reached. These measures were computed for each subject at each assessment time-point. The percentage of correct

responses was also computed for the randomized control version of the task completed at the second time-point. For percentage of correct responses, we conducted a generalized linear mixed model with group (mother-reared/peer-reared), time-point (3.5/5 years), and their interaction included as fixed effects, and subject, time-point, and session as nested random intercepts. For the cumulative score and maximum delay, we conducted a linear mixed model with group, time-point, and their interaction included as fixed effects, and subject-specific random intercepts. To compare the percentage of correct responses in the original task versus the randomized control version at the second time-point, we conducted a generalized linear mixed model with group, task (original/control), and their interactions included as fixed effects, and subject, task (original/control), and session as nested random intercepts.

The computational model was fitted separately for each subject at each assessment time-point, and for the two versions of the tasks. To compare the fitted model parameters between the two rearing groups across time, we used linear mixed models with group, time-point, and their interactions included as fixed effects, and subject-specific random intercepts. To compare the fitted parameters between the two rearing groups and tasks at the second time-point, we used linear mixed models with group (mother-reared/peer-reared), task (original/control), and their interactions included as fixed effects, and subject-specific random intercepts. To investigate whether the fitted model parameters were related to task performance, and thus to what extent the performance measures reflected involvement of working memory and inhibitory control, we used separate linear mixed models for each model parameter and performance measure in the original version across time. For percentage of correct responses, cumulative score, and maximum delay, we computed linear mixed models with model parameter (i.e.  $w_1$ ,  $\lambda_1$ ,  $w_2$ ,  $\lambda_2$ , or  $\beta$ ), group (mother-reared/peer-reared), time-point (3.5/5 years), and group by time-point interaction included as fixed effects, and subject-specific random intercepts. We then used separate linear mixed models for each model parameter and performance measure across tasks at the second time-point. For the percentage of correct responses, we fit linear mixed models with model parameter (i.e.  $w_1$ ,  $\lambda_1$ ,  $w_2$ ,  $\lambda_2$ , or  $\beta$ ), group (mother-reared or peer-reared), task (original/control) and group by task interaction included as fixed effects, and subject-specific random intercepts.

R v4.0.5 (R Core Team, 2020) was utilized to conduct all analyses presented here (see SI for package information). P-values for fixed effects and interactions were obtained using

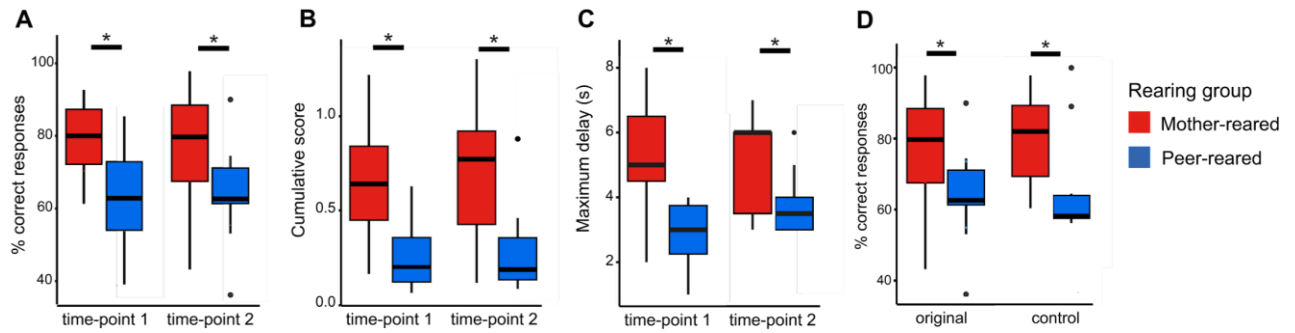
Type III Wald  $\chi^2$  tests for generalized linear models. To account for smaller sample sizes and normality violations, permutation tests (grouped by subjects) with 10,000 permutations were used to assess significance of linear model factors and to follow-up significant interactions.

## Results

### *Task performance*

We first sought to determine if task performance varied between groups and time-points by comparing each of the performance measures (percentage of correct responses, cumulative score, and maximum delay) between groups and time-points for the original version of the 'A-not-B' task. A significant main effect of group was revealed for the percentage of correct responses [ $\chi^2(1) = 9.462; p < 0.01$ ], with a higher performance for the mother-reared compared to the peer-reared group (Figure 4A). No significant main effect of time-point or group by time-point interaction was found. A significant main effect of group was also revealed for a cumulative score [ $F(1) = 12.643, p < 0.01$ ], with a higher score for mother-reared compared to peer-reared group (Figure 4B). No significant effect of time-point or group by time-point interaction was found. Finally, a significant main effect of group was found for the maximum delay [ $F(1) = 17.721, p < 0.001$ ], with a higher delay for mother-reared compared to peer-reared group (Figure 4C). Again, no significant effect of time-point or group by time-point interaction was revealed.

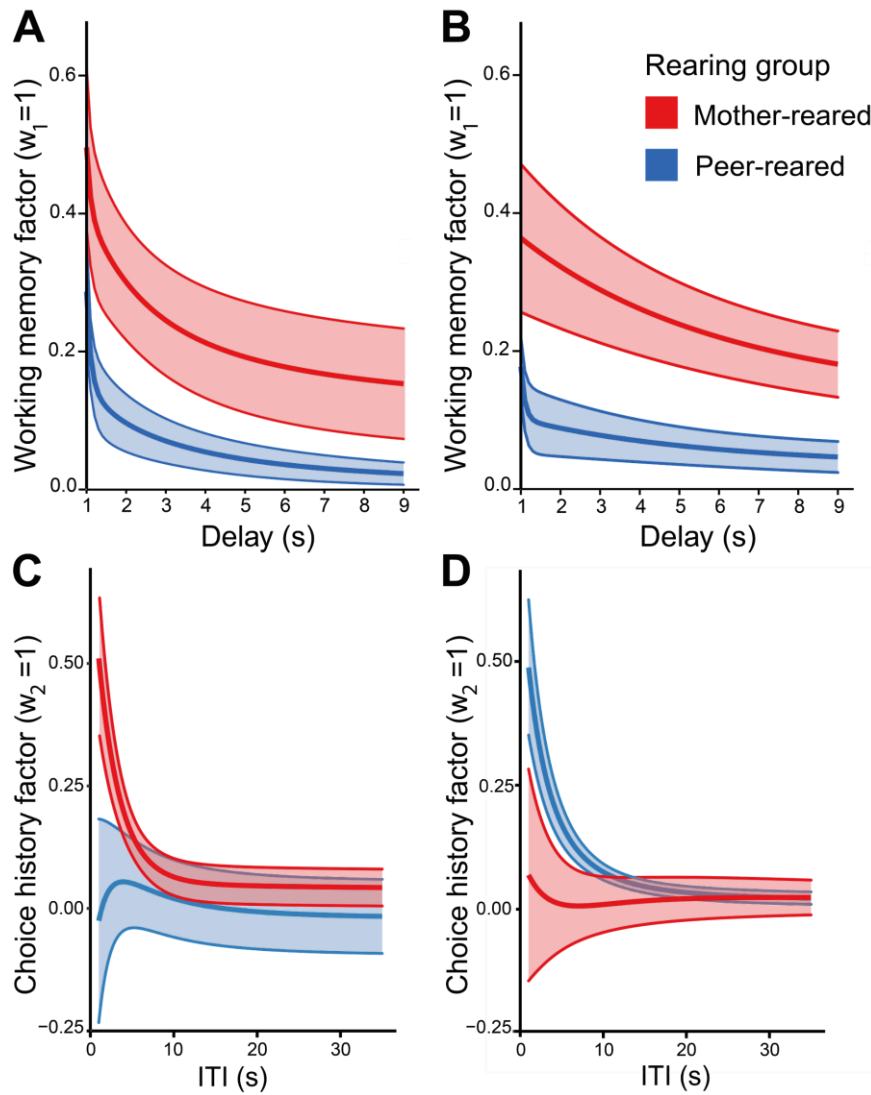
Having established that the mother-reared group had higher performance on the 'A-not-B' task than the peer-reared group at each time-point, we then compared their performance between the original 'A-not-B' task and the random control task at the second time-point. A significant main effect of group was found [ $\chi^2(1) = 6.323; p = 0.011$ ], with a higher percentage of correct responses for the mother-reared compared to the peer-reared group (Figure 4D). No significant main effect of task or task by group interaction was revealed.



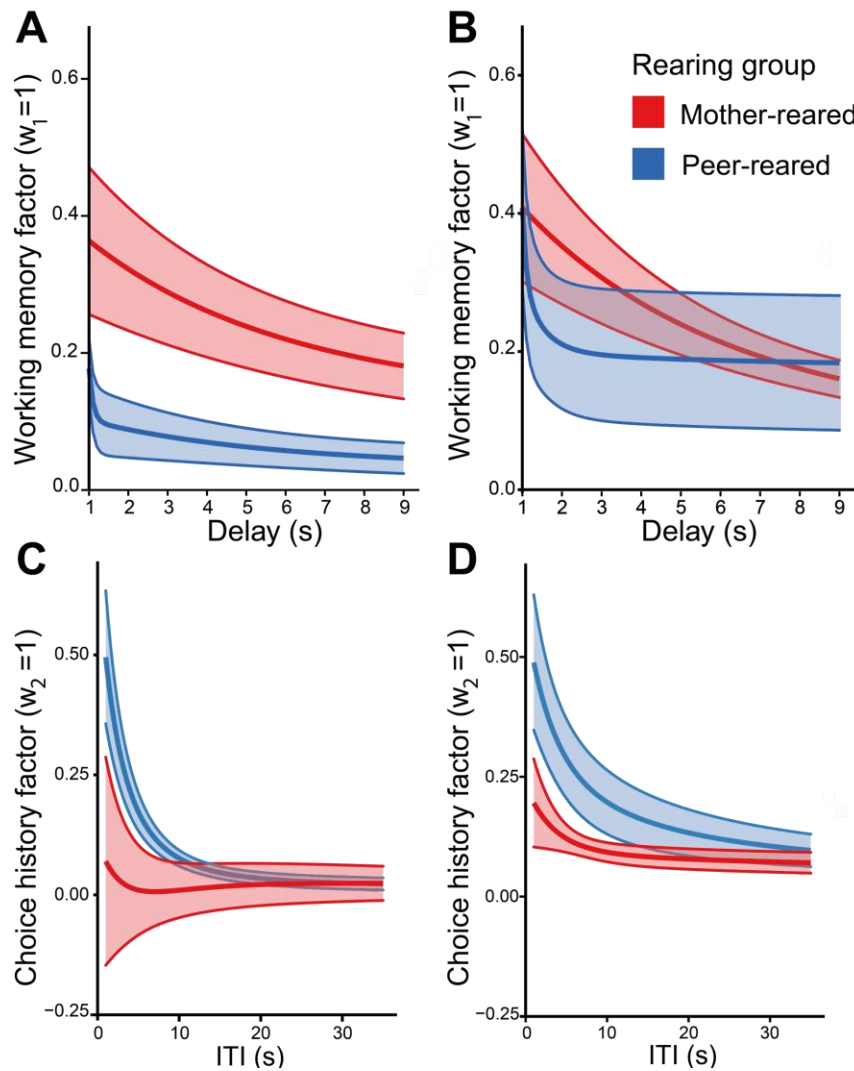
**Figure 4. Task performance.** The mother-reared group had a significantly higher percentage of correct responses (A), cumulative score (B), and maximum delay (C) in the original ‘A-not-B’ task than the peer-reared group at both time-points. Mother-reared animals also had a significantly higher percentage of correct responses in the randomized control task at the second time-point (D), and the performance of each group was not different between tasks.

### Computational model fits

In order to determine the cognitive mechanisms underlying the difference in performance between the two groups, we then compared the fitted model parameters between groups and time-points for the ‘A-not-B’ task. A significant main effect of group was revealed for working memory decay ( $\lambda_1$ ) [ $F(1) = 7.008, p = 0.014$ ], with the peer-reared group demonstrating a significantly faster rate of decay compared to the mother-reared group (Figure 5A; 5B). There was no significant effect of time-point or group by time-point interaction, and no significant differences in terms of the weight of the working memory factor ( $w_1$ ). There were no main effects of group or time-point on the weight of the choice history factor ( $w_2$ ), but a significant interaction between group and time-point was found [ $F(1) = 7.159, p = 0.021$ ], with  $w_2$  decreasing from time-point 1 to time-point 2 in mother-reared group and increasing in the peer-reared group. No significant main effects or interactions were found for choice history decay rate ( $\lambda_2$ ; Figure 5C; 5D), or choice stochasticity ( $\beta$ ).



**Figure 5.** Fitted model parameters for the original 'A-not-B' task at both time-points. A) Decay in the value of the working memory factor at the first time-point, given  $\lambda_1$ , and fixing  $w_1=1$ , for various delay durations. The solid lines represent the mean over subjects (red = mother-reared, blue = peer-reared), and the shaded areas represent the standard error. B) As in (A), for the second time-point. C) Decay in the value of the choice history factor rate at the first time-point, given  $\lambda_2$ , and fixing  $w_2=1$ , for various inter-trial intervals. D) As in (C), for the second time-point.



**Figure 6.** Fitted model parameters for the original and random control tasks at the second time-point. (A) Decay in the value of the working memory factor for the original ‘A-not-B’ task at the second time-point, given  $\lambda_1$ , and fixing  $w_1=1$ , for various delay durations. The solid lines represent the mean over subjects (red = mother-reared, blue = peer-reared), and the shaded areas represent the standard error. (B) As in (A), for the random control task at the second time-point. (C) Decay in the value of the choice history factor rate for the original ‘A-not-B’ task at the second time-point, given  $\lambda_2$ , and fixing  $w_2=1$ , for various inter-trial intervals. (D) As in (C), for the random control task at the second time-point.

We then aimed to establish if the mechanisms behind the difference in performance between groups were similar in both versions of the task by comparing their fitted model parameters between the original ‘A-not-B’ task and the random control task at the second time-point. For working memory decay rate ( $\lambda_1$ ), a significant main effect of group was revealed [ $F(1) = 5.314$ ,  $p = 0.022$ ], with the peer-reared group demonstrating a significantly faster rate of decay compared to the mother-reared group (Figure 6A; 6B). There was no significant effect of task, or a group by task interaction. Again, there were no significant

differences in terms of the weight of the working memory factor ( $w_1$ ) (Figure 6A; 6B). For choice history, a significant main effect of group was revealed, with a greater choice history factor weight ( $w_2$ ) found for the peer-reared compared to the mother-reared group [ $F(1) = 5.454, p = 0.031$ ] (Figure 6C; 6D). There was no significant effect of time-point or interaction effects. No significant main effects or interactions were found for decay rate of the choice history factor ( $\lambda_2$ ) (Figure 6C; 6D). For choice stochasticity ( $\beta$ ) there were no significant main effects or interactions.

### ***Relationship between fitted model parameters and performance measures***

Having shown that the groups vary similarly in terms of their performance in the original 'A-not-B' and random control tasks, and that the model predicts group differences in working memory decay and the influence of choice history, we then wanted to find out if these mechanisms were reflected by any of the performance measures calculated. We therefore related each fitted parameter to each performance measure for the original version of the task at both time-points. The weight of the working memory factor ( $w_1$ ), and the rate of working memory decay ( $\lambda_1$ ) predicted the percentage of correct responses [ $w_1: F(1) = 11.104, p < 0.01; \lambda_1: F(1) = 10.564, p < 0.01$ ], with higher working memory factor weight and longer working memory decay rate predicting a higher percentage of correct responses. There was no relationship between the weight of the choice history factor ( $w_2$ ), the decay rate of the choice history factor ( $\lambda_2$ ), or choice stochasticity ( $\beta$ ) and the percentage of correct responses. The cumulative score was predicted by the weight of the working memory factor ( $w_1$ ) [ $F(1) = 4.576, p = 0.038$ ], the rate of working memory decay ( $\lambda_1$ ) [ $F(1) = 17.052, p < 0.01$ ], and choice stochasticity ( $\beta$ ) [ $F(1) = 8.880, p < 0.01$ ], with higher working memory factor weight, longer working memory decay rate, less choice stochasticity predicting higher cumulative scores. There was no relationship between the weight of the choice history factor ( $w_2$ ) or the decay rate of the choice history factor ( $\lambda_2$ ) with the cumulative score. Finally, the rate of working memory decay ( $\lambda_1$ ) [ $F(1) = 19.487, p < 0.001$ ] and choice stochasticity ( $\beta$ ) [ $F(1) = 9.941, p < 0.01$ ] both predicted the maximum delay, with longer working-memory decay rate and less choice stochasticity linked to higher maximum delay. Neither the weight of the working memory factor ( $w_1$ ), the weight of the choice history factor ( $w_2$ ), nor the decay rate of the choice history factor ( $\lambda_2$ ) predicted maximum delay.



We then repeated this analysis for the original 'A-not-B' task and the random control task at the second time-point, relating each fitted model parameter to the percentage of correct responses (the cumulative score and maximum delay metrics only apply to the original task structure). The weight of the working memory factor ( $w_1$ ) [ $F(1) = 9.921, p < 0.01$ ] and working memory decay rate ( $\lambda_1$ ) [ $F(1) = 4.696, p = 0.046$ ] both predicted the percentage of correct responses, with greater  $w_1$  and longer decay rate related to a higher percentage of correct responses. The weight of the choice history factor ( $w_2$ ), the decay rate of the choice history factor ( $\lambda_2$ ), and choice stochasticity ( $\beta$ ) did not predict the percentage of correct responses.

## Discussion

This study aimed to assess the longitudinal effects of early psychosocial deprivation on executive function (EF) across adolescence and early maturity in rhesus macaques, using an 'A-not-B' task. We found that early psychosocial deprivation had a negative effect on task performance, with the peer-reared group performing worse than the mother-reared group at both assessment time-points. Furthermore, fitting a computational model of decision making enabled us to identify the mechanistic processes likely contributing to performance on the task, with results suggesting that psychosocial deprivation has long-term effects on both working memory and inhibitory control components of EF. In addition to offering important insights into the longitudinal effects of early deprivation on EF, findings also support a protracted developmental trajectory of inhibitory control in macaques that extends into adulthood. These results indicate that the mechanisms implicated in development of specific EF components are similar in macaques and humans, with specific EF components having different developmental timelines. Our study therefore also provides support for the use of macaque models to investigate the psychological and neural mechanisms through which executive function develops more generally.

Our findings provide clear evidence for the potential long-term negative impact of early psychosocial deprivation on EF in macaques. Mother-reared animals performed better on the 'A-not-B' task than peer-reared animals across adolescence (time-point 1: 3.5 years) and early adulthood (time-point 2: 5 years), which is in line with previous findings suggesting

that early psychosocial deprivation effects on childhood EF in humans can persist into adulthood (Wade et al., 2019). Analysis of the fitted model parameters revealed differences between the groups in terms of working memory, with peer-reared animals having a faster rate of working memory decay across time. A difference in terms of inhibitory control (i.e. the influence of choice history) was also found, with peer-reared subjects having a greater tendency to repeat, rather than inhibit, their previous choice in early adulthood. Notably, results from the modified random version of the task, used as a control at the second time-point (5 years), indicate that these group differences were not simply due to learning the structure of the original 'A-not-B' task. These effects on specific components of EF are in keeping with evidence that adversity in the form of early deprivation may have a particularly severe impact on working memory and inhibitory control in humans (e.g. Johnson et al., 2021).

Notably, analysis of the fitted model parameters suggests that early psychosocial deprivation was linked to poor working memory in adolescence and early adulthood, but to weaker inhibitory control in early adulthood only. This could be due to several different factors. One possibility is that the performance directly impacted the ability of the task to correctly assess inhibitory control. According to Diamond et al. (Diamond & Goldman-Rakic, 1989), the 'B' error (i.e. an incorrect response after switching the hiding position) occurs only when performance is accurate enough. This would mean that inhibitory control is only assessed correctly when accuracy is relatively high. Many studies use a criterion for subject inclusion where the participant has to be successful in at least one 'B' trial to be included in analysis (e.g. Holmboe et al., 2018). We also used this criterion, and the model successfully predicted the same proportion of responses for both rearing groups despite their differences in performance (see SI). It is therefore unlikely that the differences in the fitted model parameters would be due to performance differences. Another possibility is that working memory and inhibitory control follow different developmental trajectories. For example, evidence shows that inhibitory control starts to decline later (around 35 years) than working memory in human adults (Ferguson et al., 2021), and in macaques, evidence suggests that working memory is mature even at pre-puberty whereas inhibitory control is not (Zhou et al., 2016) . However, a lack of longitudinal studies that focus on both working memory and inhibitory control does not allow any clear conclusion to be made. Based on our findings, we propose that while early psychosocial deprivation may impact both aspects of EF, their

developmental trajectories after exposure likely differ. Peer-reared animals could have accelerated development of inhibitory control compared to mother-reared, then during adolescence, they are less flexible and do not improve. On the contrary, working memory may be impaired or accelerated at an earlier stage of development, with a protracted and stable negative effect of early psychosocial deprivation then seen across the transition from adolescence to adulthood. These differing trajectories could be explained by distinct underlying brain networks that are differentially impacted by early psychosocial deprivation. Confirming this hypothesis now requires more studies assessing neural measures development and actual link to behaviour across various stages of development.

Importantly, the inhibitory control parameters of the computational model (i.e. the influence of choice history), did not predict any of the performance measures, including the cumulative score and maximum delay, which are thought to account for both inhibitory control and working memory EF components. On the contrary, the working memory parameters predicted all performance measures. This suggests that the performance measures used in previous research mainly capture the influence of working memory on behaviour. However, using the computational model, it was possible to assess the contribution of both working memory and inhibitory control separately using an 'A-not-B' task. These findings are in line with the recent suggestion that proper assessment of inhibitory control in the first years of life is difficult using 'A-not-B' and similar tasks because of the high demands of working memory necessary to complete such tasks (Hendry et al., 2021; Holmboe et al., 2018). Fitting of computational models could thus help us to understand if EF follows an unitary construct in infancy or if different components can already be distinguished at a very early stage of development still using this task (Fiske & Holmboe, 2019), and how these factors can lead to individual differences related to both positive and negative outcomes. Our results suggest that the 'A-not-B' task does correctly assess inhibitory control, but this EF component is not reflected by the measures of performance used in the previous literature.

There are a few limitations to the present study that should be acknowledged. First, due to the sample size, it is difficult to account for inter-individual variability within the two groups and the results may thus not be generalizable. Second, we did not have any time-points pre-puberty, which would be necessary to fully examine developmental trajectories of EF development after exposure to early psychosocial deprivation. Third, we only had the control

version of the task at the second assessment time-point (5 years). It will be important in future research to replicate these results with careful controls in larger samples, and at time-points covering multiple key transition periods in development.

This study also has several strengths. First, we assessed the effect of early psychosocial deprivation on EF development at two time-points covering a key transition period (i.e. adolescence into early adulthood). Second, our sample included two groups of macaques exposed to different early social and highly controlled environments. Third, all assessments were conducted with the monkeys remaining in their home enclosure without the addition of invasive and stressful procedures, which also makes results more comparable to those from human studies (Dettmer et al., 2015). Finally, the use of a computational model enabled the distinction between specific aspects of EF. This approach could be of great use in future longitudinal assessment of EF, especially when including a wide range of key developmental transition points.

To conclude, results from this study demonstrate that early psychosocial deprivation is associated with long-term effects on EF, which are apparent in adolescence and persist into adulthood. The use of a computational model of decision-making to disentangle mechanisms underlying performance on the 'A-not-B' task provides an alternative way to analyse the data from such tasks, and may be of specific interest for developmental research, which is often defined by a lack of precise measurement tools. In the future, computational approaches such as that used here can easily be adapted to other EF tasks, with the results then more easily linked to specific aspects of neural development and related cognitive mechanisms than classic behavioural measures alone. Such research involving assessment of brain development is essential for clarifying how early deprivation affects EF over the lifespan, and identifying the factors that confer risk for or resilience against poor developmental outcomes. This will be critical for design of more effective treatments and interventions that target individuals more at risk for developing impairments in specific aspects of EF and associated difficulties after exposure to early psychosocial deprivation.

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## Supplementary information

### **Methods**

#### **Subjects**

All subjects were born and raised at the *Laboratory of Comparative Ethology at the National Institutes of Health, US*. Peer-reared animals were raised in a nursery with access to same-aged peers. See Shannon et al. (1998) for more information on the peer-rearing protocol. Rearing procedures were approved by the NICHD and the University of Maryland Animal Care and Use Committee, and adhered to the NIH Guide for the Care and Use of Laboratory Animals. Animals were relocated to their current location at the *Rousset Primatological Station, CNRS, France* at two years of age, and are housed together. As part of a wider longitudinal study, animals are temporarily relocated once a year to a nearby location in groups of 5-6 mixed mother- and peer-reared animals. All animals were kept alive at the end of the study.

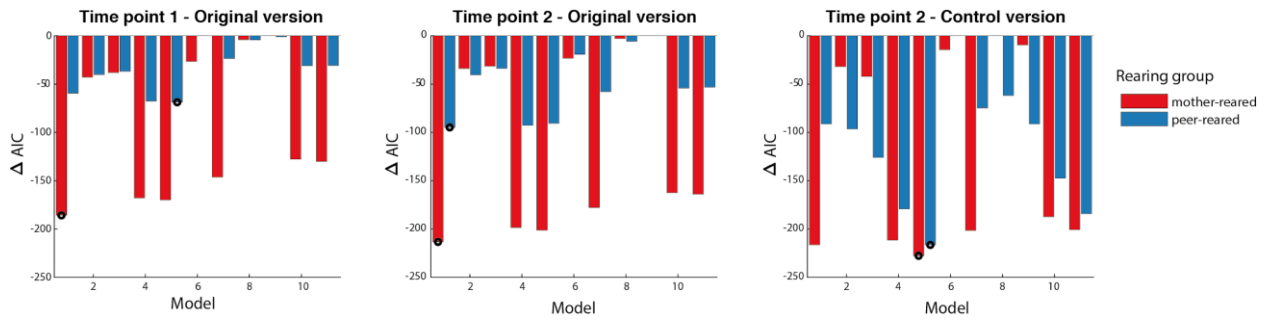
#### **Video coding**

We coded a number of parameters offline from the video recordings made of each subject during the testing sessions. These included the actual length of the delay periods (i.e. from the moment the experimenter showed the food to the subject, to the moment the clear panel was removed to enable the subject to reach for the wells), inter-trial-interval (ITI) lengths, position of the subject in the testing enclosure during each trial, and other behaviours during and between trials that may have affected performance, such as locomotion, pacing, anxiety (i.e. self-scratch, self-groom, yawn), vocalizations, and threatening, fearful, or affiliative gestures. These behaviours were coded as being present or not during each trial and ITI. A random 15% of videos were coded by two researchers at each time-point to establish reliability for the original version of the task, and for the control version of the task at the second-time point (5 years). All reliability scores obtained between coders were very strong (i.e. all  $\kappa = 0.86-1.00$ ).

#### **Computational model**

We tested 11 different computational models that differed in terms of the factors that contributed to the decision variable,  $z$ :

- 1) Working memory :  $z_t = w_1 S_t e^{-\lambda_1 d_t}$ , where  $w_1$  is the weight of this factor when the delay is 0,  $S_t$  is the side that food was hidden on in trial  $t$  (left = -1, right = 1), and  $d_t$  is the delay
- 2) Previous choice:  $z_t = w_2 R_{t-1} e^{-\lambda_2 (i_t + d_t)}$ , where  $w_2$  is the weight of this factor when the inter-trial interval and delay is 0,  $R_{t-1}$  is the response made on the previous trial (left = -1, right = 1), and  $i_t$  is the inter-trial interval before this trial.
- 3) Previous two choices:  $z_t = w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)})$
- 4) Working memory and previous choice:  $z_t = w_1 S_t e^{-\lambda_1 d_t} + w_2 R_{t-1} e^{-\lambda_2 (i_t + d_t)}$
- 5) Working memory and previous two choices:  $z_t = w_1 S_t e^{-\lambda_1 d_t} + w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)})$
- 6) Expected reward:  $z_t = w_3 (v_{R,t} - v_{L,t})$ , where  $w_3$  is the weight of this factor,  $v_{R,t}$  is the expected reward at time  $t$  for choosing right, and  $v_{L,t}$  is the expected reward at time  $t$  for choosing left. Expected reward for each side was updated using the standard Rescorla-Wagner rule:  $v_{c,t+1} = v_{c,t} + \alpha (\hat{v}_{c,t} - v_{c,t})$ , where  $v_{c,t}$  is the expected reward for side  $c$  at time  $t$ ,  $\alpha$  is the learning rate, and  $\hat{v}_{c,t}$  is the actual reward received for choosing side  $c$  at time  $t$ .
- 7) Working memory and expected reward:  $z_t = w_1 S_t e^{-\lambda_1 d_t} + w_3 (v_{R,t} - v_{L,t})$
- 8) Previous choice and expected reward:  $z_t = w_2 R_{t-1} e^{-\lambda_2 (i_t + d_t)} + w_3 (v_{R,t} - v_{L,t})$
- 9) Previous two choices and expected reward:  $z_t = w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)}) + w_3 (v_{R,t} - v_{L,t})$
- 10) Working memory, previous choice, and expected reward:  $z_t = w_1 S_t e^{-\lambda_1 d_t} + w_2 R_{t-1} e^{-\lambda_2 (i_t + d_t)} + w_3 (v_{R,t} - v_{L,t})$
- 11) Working memory, previous two choices, and expected reward:  $z_t = w_1 S_t e^{-\lambda_1 d_t} + w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)}) + w_3 (v_{R,t} - v_{L,t})$



**Figure S1:** *Model comparison.* Akaike information criterion (AIC) for each model relative to the worst model for both groups at each assessment time-point and task version. Filled circles represent the models with the lowest AIC.

Model comparison was performed using the Akaike information criterion (AIC; Akaike, 1973), a metric that captures the trade-off between model goodness of fit and complexity. Lower AIC (relative to the worst model), indicates that the model better fits the data without being so complex that it overfits it. The sum of AIC for each subject was compared for each assessment time-point and task (Figure S1). Model 1 had the lowest AIC for the mother-reared group at time-points 1 and 2 and the peer-reared group at time point 2. Model 5 had the lowest AIC for the peer-reared group at time-point 1 and for both groups in the random version of the task. We therefore selected model 5 for the main analyses as it includes all the terms from model 1, and terms for the influence of the previous two choices.

### **Data analysis**

R v4.0.5 (R Core Team, 2020) and the lme4 v1.1-27.1 (Bates et al., 2015), lsmeans v2.30.0 (Lenth, 2016), predictmeans v1.0.6 (Luo et al., 2021), car v3.0.11 (Fox, Weisberg, 2019), doBy (Søren, Halekoh, 2016), and ggplot2 (Wickham, 2016) packages were utilized to conduct the analyses.

#### ***Data pre-processing:***

To check whether any coded behaviours influenced the ability of any of the 11 tested computational model to predict the responses of the subjects, we used linear mixed models with the maximum of correctly predicted responses over all model versions as the outcome variable, and with each behaviour (e.g. locomotion during trials, locomotion during ITI, anxiety during trials, etc.), group (mother-reared/peer-reared), and their interaction included as fixed effects; each behaviour (e.g. locomotion during ITI) as random slope and

subject, year (3.5/5 years), and session (1/2) as random intercepts were included as random effects. The only behaviour found to impact the ability of the model to predict the choices of the subject was locomotion during the trials, with a significant main effect of locomotion [ $F(1) = 4.671, p = 0.017$ ]. Therefore, we excluded all trials in which locomotion occurred, and in which the ITI was more than 2.5 standard deviations above the mean. We set a threshold of 25 trials minimum per subject. This resulted in one mother-reared subject being excluded from the analysis of the original task at the first time-point (3.5 years), and from analysis of the randomized control version of the task at the second time-point (5 years).

To investigate potential differences between rearing groups in terms of ITI duration in the original task at both time-points, we then used a linear mixed model with group (mother-reared/peer-reared), year (3.5/5 years), and their interaction included as fixed effects, and subject, year (3.5/5 years), and session (1/2) included as nested random intercepts. No significant main effects of group or year, or group by year interaction were found. To investigate potential differences in ITI lengths at the second time-point (5 years) in the original and control versions of the task, we again used a linear mixed model with group (mother-reared/peer-reared), task (original/control), and their interaction included as fixed effects, and subject, task (original/control) and session (1/2) as nested random intercepts. No significant main effects of group, or task or group by task interaction were found. Permutation tests (grouped by subjects and block within session and task) with 10,000 permutations were used to assess significance of linear model factors.

***Trial exclusion:***

Mean trials included for mother-reared animals were as follows: original task at the first time-point (3.5 years),  $M = 44.63, SD = 6.36$ ; original task at the second time-point (5 years),  $M = 47.1, SD = 2.96$ ; control task at the second time-point (5 years),  $M = 45.2, SD = 5.69$ . Mean trials included for peer-reared animals were as follows: original task at the first time-point (3.5 years),  $M = 44.$



3, SD = 5.61; original task at the second time-point (5 years), M = 47.3, SD = 4.49; control task at the second time-point (5 years), M = 44.2, SD = 6.17.

## Results

Descriptive statistics can be found in Table 1.

**Table 1:** Behavioral measures of performance in original and control version of ‘A-not-B’ task. Percentage of correct responses (M and SD) is the proportion of correct trials out of all trials completed. Cumulative score (M and SD) is the sum of all successful change trial delays and then divided by the number of total trials completed. Maximum delay (M and SD) is the maximum observed delay period (seconds) coded from the videos.

Group	Mother-reared	Peer-reared
<i>Percentage of correct responses</i>		
3.5 years (original)	0.787 (0.105)	0.625 (0.146)
5 years (original)	0.77 (0.171)	0.642 (0.14)
5 years (control)	0.805 (0.132)	0.661 (0.154)
<i>Cumulative score</i>		
3.5 years (original)	0.643 (0.316)	0.265 (0.204)
5 years (original)	0.712 (0.4)	0.279 (0.244)
<i>Maximum delay</i>		
3.5 years (original)	5.181 (1.778)	2.8 (1.135)
5 years (original)	5.2 (1.619)	3.8 (1.032)

### Proportion of responses predicted by the computational model

To check whether the computational model correctly predicted a different amount of responses between the two groups, we used linear mixed models with group (mother-reared/peer-reared) included as fixed effects, and subject-specific intercepts as a random effect. A permutation test was performed on the linear mixed models with 10,000 permutations (grouped by subject). No significant effect of group on the proportion of responses correctly predicted by the computational model was found.

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## **CHAPTER 4.**

**Structural brain development and executive function in macaques exposed to early psychosocial deprivation: Longitudinal effects across adolescence into adulthood**

## Introduction

Early social adversity (ESA) involves violations in the early expectable caregiving environment (Katie A. McLaughlin & Sheridan, 2016; Wade et al., 2019), and has been linked to poor development in numerous domains (Johnson et al., 2021a; Luo et al., 2021; Oeri & Roebbers, 2022; B. Zhang, 2017). Psychosocial deprivation represents one model of ESA that has received particular attention in previous research, especially in the form of early institutionalization. Early institutional rearing involves the separation of an infant from their primary caregivers, and is often followed by a lack or absence of socio-cognitive input from any regular caregiving figure. Early institutionalization is associated with negative long-term outcomes such as poor academic performance, occupational functioning, and social competence (Beckett et al., 2007; Cáceres et al., 2021; Penny Roy et al., 2004; Sonuga-Barke et al., 2017), as well as increased risk for psychiatric disorders such as mood and substance use disorders (Bos et al., 2011; Humphreys et al., 2020; van IJzendoorn et al., 2020; Zeanah et al., 2009). Increased prevalence of ADHD (Bos et al., 2011; Golm et al., 2020; Tibu et al., 2016) and quasi-autistic like behaviours (Levin et al., 2015; Rutter et al., 2007; Stein et al., 2015) have also been described in the context of early institutionalization. To design more effective early interventions and treatments for individuals who experienced early psychosocial deprivation, we now need to increase understanding of the factors conferring risk and resilience after such experience. This will require longitudinal studies investigating the specific neurocognitive mechanisms through which different poor outcomes arise after exposure to such adverse early experience, especially over important transitions later in development such as adolescence.

In terms of cognitive mechanisms, institutional rearing has been linked to abnormal threat and emotional processing (J. Bick et al., 2017; Tottenham & Sheridan, 2010), and notably, is a form of ESA most often associated with problems in executive function (EF) (Bos et al., 2009; Merz et al., 2016; Wade et al., 2019). EF refers to a group of cognitive processes that underlie the organization and control of goal-directed behaviour, and is often divided into three components: working memory, inhibitory control, and cognitive flexibility (Friedman & Miyake, 2017; Miyake et al., 2000). EF impairments play an important role in many of the poor outcomes linked to early institutionalization, including academic success and risk for internalizing and externalising psychopathology (Buzzell et al., 2020; Merz et al., 2016; Wade

et al., 2020). EF deficits are also key features of neurodevelopmental disorders associated with psychosocial deprivation (e.g. ADHD) (Friedman & Robbins, 2022; Tibu et al., 2016). Previous institutionalization has been linked to EF deficits in childhood (Hostinar et al., 2012) and adolescence (Wade et al., 2019), with children who spent more than two years in an institution demonstrating worse EF compared to those who spent less than two years in institutional care (Roy et al., 2000). Institutional rearing may have particularly severe impacts on working memory and inhibitory control components of EF (Fox et al., 2011; Johnson et al., 2021; Massera, *in press*; McDermott et al., 2013; Wade et al., 2019), however, far less investigation into the effects of institutionalization on EF has been conducted so far compared to research on strictly emotional and social processes. Therefore, much remains unknown about the long-term trajectories of EF after early psychosocial deprivation. Critically, this includes the neurobiological mechanisms through which poor EF arises and results in the emergence of dysfunctional behaviour and psychopathology.

Evidence for poor outcomes related to early psychosocial deprivation being linked to specific aspects of brain development in humans is growing (Holz et al., 2023; McLaughlin et al., 2014; Tottenham, 2020). For example, it has been shown that the prefrontal cortex (PFC) plays a central role in EF (Diamond, 2002; Fiske & Holmboe, 2019; Friedman & Robbins, 2022), with structural and functional differences in PFC found consistently in those exposed to early institutionalization (Hodel et al., 2015; Mackes et al., 2020; Sheridan et al., 2022). Although the PFC is functional from infancy, it is one of the last brain regions to reach full maturity (Fiske & Holmboe, 2019), undergoing significant development during adolescence (Caballero & Tseng, 2016; Kolb et al., 2012; Spear, 2000). As such, adolescence is proposed as a particularly important sensitive period for the refinement of EF (Larsen & Luna, 2018; Schalbetter et al., 2022). Importantly, maturation of the frontal lobe does seem to parallel known improvements in EF across development, although relatively few studies have examined this relationship explicitly over time (Fiske & Holmboe, 2019; Werchan & Amso, 2017).

As well as more immediate effects on neurocognitive development in infancy and early childhood, early social experience may have delayed developmental effects. These are often referred to as " sleeper effects " or an " incubation period " (Lupien et al., 2009; Maurer et al., 2007; Merz & McCall, 2010). For example, institutionalized children who do not exhibit externalizing psychopathology in childhood, i.e. symptoms of defiant or conduct disorders,

have been found to demonstrate such symptoms in early adolescence (McGoron et al., 2012; Zeanah et al., 2009). This suggests that early institutional experiences may affect the development of certain skills and dispositions that become more important at later developmental stages, possibly under the influence of additional stressful and demanding environmental factors associated with adolescence (Zeanah et al., 2011). However, much more research is needed to fully understand the potential delayed impact of early experiences on development of processes such as EF during adolescence and its underlying neural bases.

Beyond the PFC in isolation, EF and its various components such as working memory and inhibitory control, relies on connectivity of the PFC with other brain regions for the integration and control of cognitive representations (Constantinidis & Klingberg, 2016; Fiske & Holmboe, 2019; Menon & D'Esposito, 2022; Nowrangi et al., 2014; Smolker et al., 2015). Distinct and overlapping neural networks involving PFC likely underly the emergence of general and specific components of EF, with the protracted developmental trajectory of EF following a different course for different components (Tervo-Clemmens et al., 2022). In particular, separately and in interaction, fronto-parietal and fronto-striatal circuits are thought to play an essential role in EF across development (Darki et al., 2020; Darki & Klingberg, 2015a; Goddings et al., 2021; Morein-Zamir & Robbins, 2015), with striatal circuits playing an increasingly important role in adolescence and adulthood (Crone et al., 2016; Ojha et al., 2022; Simmonds et al., 2014) and having more protracted development. Although cortico-cortical connectivity such as that in the fronto-parietal network, which is strongly implicated in EF (Fiske & Holmboe, 2019; Goddings et al., 2021; Nowrangi et al., 2014; Yao et al., 2020), has traditionally been the main focus of EF research, findings increasingly demonstrate that subcortical regions are also vitally important. For example, Webb et al. (2020) found that deficits in fronto-striatal white matter microstructure was negatively associated with EF, with this association becoming stronger with age between early and mid-adulthood. Additionally, changes in ventral fronto-striatal white matter tracts are correlated with the development of inhibitory control throughout childhood and adolescence (Liston et al., 2006), with the caudate nucleus activated during working memory tasks in children (Klingberg et al., 2002; Ziermans et al., 2012) and adults (Postle & D'Esposito, 2003). White matter microstructure in fronto-striatal tracts has also been related to future working memory in adolescence and into early adulthood, with caudal activity predicting future working memory capacity (Darki &

Klingberg, 2015a). However, studies so far have been primarily cross-sectional, and have not fully clarified the neural dynamics underlying changes in working-memory and inhibitory control across development (Darki & Klingberg, 2015a; Goddings et al., 2021; Vestergaard et al., 2011).

There has been relatively little examination of the impact of early psychosocial deprivation on the neurophysiological substrates of EF specifically, or the actual relationship between brain development and performance on EF tasks. Using EEG, institutionalized children were found to have higher theta power and lower alpha and beta power at 22 months of age compared to a control group, with this pattern having previously being linked to ADHD and learning disorders (Marshall & Fox, 2004; K. A. McLaughlin et al., 2010). Institutionalized individuals continue to display an atypical pattern of neural activity found in childhood, whereby they demonstrate lower alpha power and higher theta power at 16 years compared to controls (Debnath et al., 2020; Vanderwert et al., 2010, 2016). Such reduced alpha power and elevated theta power is proposed to reflect a deficit in cortical maturation in institutionalized children (Debnath et al., 2020), which is presumably linked to cognitive function. At 12 years, EEG has also been used to show that institutionalized children demonstrate worse inhibition of planned actions, with larger P2 and smaller N2 event-related potential (ERP) component amplitudes moderating the association between psychosocial deprivation and symptoms of externalizing behavior (Lamm et al., 2018). A couple of functional MRI studies have shown that worse cognitive control in preschool children exposed to early institutionalization is related to altered prefrontal resting-state connectivity (Demir-Lira et al., 2016), and that stronger coupling between the ventral striatum and the medial prefrontal cortex is associated with parent-reported social problems in previously institutionalized adolescents (Fareri et al., 2017).

In terms of structural brain development, a few studies have also used anatomical and diffusion MRI to investigate the relationship between institutional rearing, EF development, and ADHD symptoms (Johanna Bick & Nelson, 2015; Demir-Lira et al., 2016; Mackes et al., 2020; Sheridan et al., 2022; Wade et al., 2019). In these studies, deprivation was associated with reduced grey and white matter volume, as well as cortical thickness in prefrontal regions (ACC, IFG, mPFC), which in turn, mediated the relationships between deprivation, lower IQ, and ADHD symptoms in childhood (Katie A. McLaughlin et al., 2014). However, thicker cortex

in prefrontal regions in adolescents and young adults exposed to early psychosocial deprivation has been related to worse behavioural outcomes and increased risk for psychopathology, with reduced thinning for exposed individuals compared to non-exposed during adolescence and early adulthood (Mackes et al., 2020; Sheridan et al., 2022).

Although relatively few studies have looked at *structural* brain connectivity after psychosocial deprivation in humans, the use of techniques such as diffusion MRI and diffusion tensor imaging (DTI) for studying white matter connecting different brain regions related to EF in future research will be extremely important, with EF involving multiple functions supported by multiple brain regions that are connected structurally via different brain networks (Goddings et al., 2021). Additionally, myelination, which is critical for neural circuit formation (Malave et al., 2022), may be an aspect of structural brain development severely impacted by ESA (Islam & Kaffman, 2021; Lutz et al., 2017; Teissier et al., 2019). One recent study that used DTI to examine the effects of institutionalization on structural brain connectivity during adolescence found reduced integrity in the superior longitudinal fasciculus (SLF), a white matter tract connecting the prefrontal and parietal cortices (Sheridan et al., 2022) and linked consistently to EF (Koshiyama et al., 2020; Vestergaard et al., 2011). Early institutionalization has also been found to impact development of fronto-striatal tracts from childhood until adolescence, with reduced white-matter integrity in the corona radiata (CR), the internal capsule (IC), and the external capsule (EC) (Bick et al., 2017; Bick & Nelson, 2016; Sheridan et al., 2022).

Because longitudinal studies of early adversity assessing both neural and cognitive changes over time are rare, many questions remain about the trajectories of neurocognitive development linked to risk or resilience after early psychosocial deprivation (Goddings et al., 2021), especially in terms of EF. The use of a nonhuman primate (NHP) model such as rhesus macaques (*Macaca mulatta*) could be very helpful to address these outstanding questions. Macaque monkeys are one of the closest species to humans in terms of genetics, physiology, and neural organization, and have an extended period of development comprising distinct infant, juvenile (pre-adolescent and adolescent), and adult stages (Phillips et al., 2014; Wang et al., 2020). Like humans, their early social environment also consists predominantly of mother-infant interactions (Maestriperi et al., 2009). The use of a macaque model can also help address some limitations defining developmental studies with humans, such as a lack of



control over the early environment, very long developmental time-frames, and difficulty in tracking neural mechanisms underlying cognitive development.

Research focused on cognitive development in macaques suggests that it parallels that in humans (Hara, 2012; Gray, 2019), and in adult macaques, EF relies on the same brain networks (Constantinidis & Klingberg, 2016; Lacreuse et al., 2020; Oguchi et al., 2021). The few studies that have looked at effects of early psychosocial deprivation on cognitive function in macaques have produced mixed findings (e.g. Murphy & Dettmer, 2020; Sánchez et al., 1998), with research comparing ESA-exposed versus non-ESA-exposed animals especially rare. Additionally, these studies only looked in infancy, and no studies have examined EF specifically, or its different components explicitly after psychosocial deprivation in macaques. However, in our recent work (Massera et al., *in press*; presented in Chapter 3 of this thesis) looking at macaque EF in adolescence and early adulthood, we showed that early psychosocial deprivation is associated with worse overall EF performance in macaques exposed to early psychosocial deprivation. Using a computational model of decision making, we were also able to show that poor performance in these animals likely reflected worse working memory across adolescence into adulthood, as well as worse response inhibition as they reached maturity. Longitudinal studies tracking both EF and brain development across key developmental transitions such as adolescence are now required to elucidate the neural mechanisms through which such differences in EF arise.

Accordingly, the research presented here was designed to investigate how structural brain development in PFC and related networks may underlie EF deficits longitudinally in macaques exposed to early psychosocial deprivation. We used anatomical MRI to measure cortical thickness in dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC) at two time-points corresponding to the adolescent (3.5 years) and early adulthood (5 years) project time-points (i.e. when EF was assessed in both the peer-reared and mother-reared animals). Both dlPFC and vlPFC are subregions of PFC often linked to EF components such as working memory and inhibitory control (e.g. Fiske & Holmboe, 2019; Hertrich et al., 2021; Nejati et al., 2018; Nelson & Guyer, 2011; Petrides, 2005). Additionally, using diffusion MRI/DTI at the same time-points (3.5 and 5 years), we assessed integrity of white-matter tracts involved in EF circuitry (Goddings et al., 2021), and known to be affected by early social adversity (Fareri et al., 2017; Ojha et al., 2022; Sheridan et al., 2022). Measures of EF from the behavioural task (Chapter 3)

were related to grey and white matter ROIs across time. We hypothesized that: i) cortical thickness in PFC regions (vlPFC and dlPFC) would decrease over time, but would be greater in the peer-reared versus mother-reared group; ii) integrity in fronto-parietal and fronto-striatal white matter tracts would increase over time, but would be lower in the peer-reared versus mother-reared group; iii) EF measures would be related to cortical thickness in dlPFC and vlPFC, and white matter integrity in fronto-parietal and fronto-striatal tracts, with better EF linked to thinner cortex and higher integrity, respectively; iv) working memory and response inhibition would be related to both overlapping (e.g. SLF) and distinct patterns of structural connectivity and cortical thickness in these different regions and circuitry; and v) cortical thickness and white matter integrity would modulate the relationship between psychosocial deprivation and EF across time, with fronto-striatal tracts having greater effects in adulthood compared to adolescence.

## Methods

### *Subjects*

The sample consisted of 21 Rhesus macaque monkeys (*Macaca mulatta*), 11 mother-reared (five female) and 10 peer-reared (six female). Subjects were aged around 3.5 years at the first assessment time-point (mother-reared; M = 44.97 months, SD = 3.41 months: peer-reared; M = 44.81 months, SD = 3.32 months) and 5 years at the second assessment time-point (mother-reared; M = 59.37 months, SD = 3.28 months: peer-reared; M = 59.47 months, SD = 3.12 months). Subjects were housed at the *Institut des Sciences Cognitives Marc Jeannerod*, CNRS, during the assessment period in mixed mother- and peer-reared social groups of 5–6 animals (see SI for more information about rearing protocol). Although new instances of maternal separation in monkeys for research is largely prohibited, it was decided that further study of this particular sample of juvenile animals was the most ethical course of action. Due to the closure of the centre in the US where animals were born and lived for the first two years of life, it was agreed that our team at the ISC-MJ would receive these animals rather than allow them to be euthanized for medical research whereby effects of their early social experiences would not be considered; and consequently, would fail therefore to maximize the scientific benefit that could be derived from this existing sample. Every effort

has been made to ensure that these animals now live in the most enriching environment possible, including their social environment, and the tasks included in the current study were designed to be as noninvasive as possible. All housing and procedures conformed to current guidelines concerning the care and use of laboratory animals (European Community Council Directive No. 86-609), and were approved by our local ethics board, Comité d’Ethique Lyonnais pour les Neurosciences Expérimentales (CELYNE) C2EA #42 (03.10.18), and the French Ministry of Research (10.10.18); project reference APAFIS#15091\_2018071014483295\_v2. All reporting here conforms to the recommendations in the ARRIVE Guidelines for Reporting Animal Research.

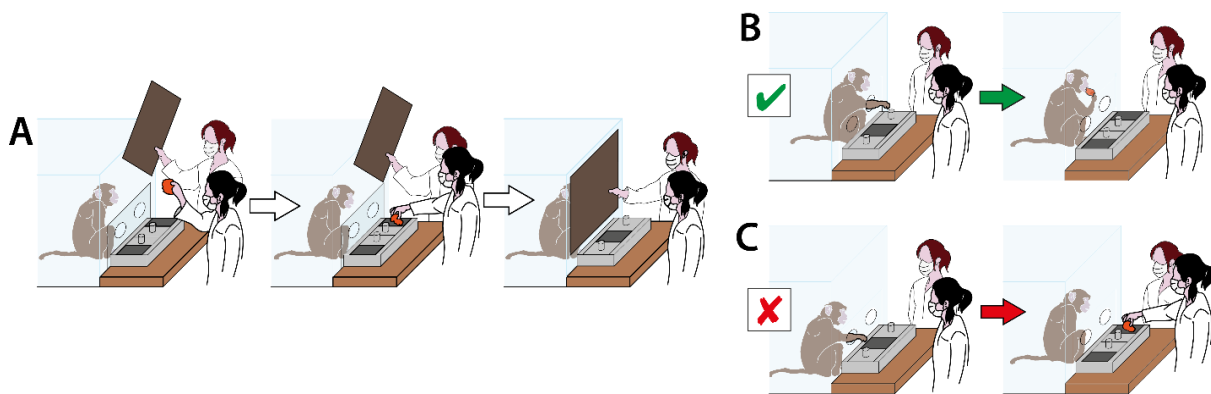
### ***‘A-not-B’ task set-up and procedure***

To measure EF, subjects completed a ‘A-not-B’ task at both time-points. Subjects were placed in a designated testing area within their home enclosure for the experiment. The testing area was 87 cm x 100 cm x 120 cm with a transparent front panel. The subjects were familiar with the process of being placed in the testing area and with the equipment used in the task. There were two holes in the transparent front panel of the testing area, which allowed the subjects to access objects on a table outside the enclosure. A transparent board was used to block the holes at certain times during the task. A box with two wells and sliding doors was placed on the table in front of the holes. The wells were 11.2 cm in diameter and were spaced 18 cm apart. Two experimenters were present during the task, with one facing the subject and the other standing on one side of the table. The side that the second experimenter stood on was counterbalanced across subjects and sessions (see Figure 1 for set-up).

During a trial (Figure 1), one experimenter presented a piece of food to the subject and placed it in one of the wells, then covered both wells with sliding doors. The trial only proceeded if the subject looked at the food when it was presented and when it was hidden. After a delay period during which the subject's physical and visual access to the wells was blocked, the opaque screen and transparent board were removed and the subject was allowed to reach for the wells. If the subject reached for the correct well, they were allowed to eat the food. If they reached for the wrong well, the correct well was opened to show them the food. If the subject touched both wells, did not respond, or the response was unclear, the trial was repeated. The location of the food was changed after the subject reached for the

correct well on two consecutive trials. Each subject completed two testing sessions at each assessment time-point, with a maximum of 25 trials per session. The delay period was adjusted based on the subject's performance. The trial was live-coded by one experimenter and recorded by a camera.

To assess differences between general EF performance between the two rearing groups, we computed a 'cumulative score' based on previous developmental studies using a comparable 'A not B' paradigm; i.e. the sum of successful change trial delays divided by the number of total trials completed (Holmboe et al., 2008), as a measure of performance.

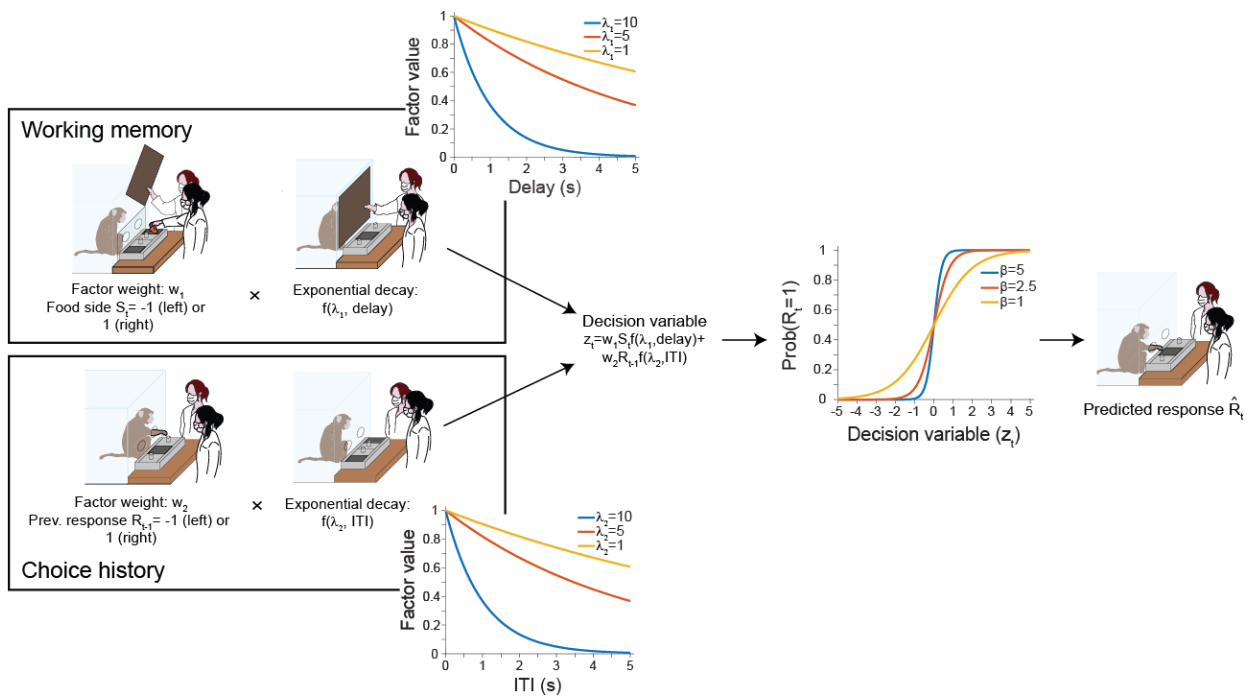


**Figure 1. Task procedure.** The series of images show the sequence of a single trial. In the first three images (A) Experimenter 1 presents the food to the subject and places it in the well. Experimenter 2 then blocks the subject's vision while a delay period occurs. The top right images (B) show a 'correct' choice, where the subject reaches for the well with the food and consumes it. The bottom right images (C) show an 'incorrect' choice, in which the subject selects the empty well and Experimenter 1 points out where the food was actually located.

### ***Video coding***

During the testing sessions, video recordings were made of each subject and a number of parameters were coded from these recordings offline. These parameters included the actual length of the delay periods (which may have differed slightly from the intended duration) in seconds, and the length of the inter-trial intervals (ITIs) in seconds (see SI).

## Computational model



**Figure 2. Computational model architecture.** The model included two decaying memory traces: one for the location of food (shown in the top left plot, where higher decay rates correspond to a faster diminishment of working memory influence) and one for the previous choice made (shown in the bottom left plot, where higher decay rates correspond to a faster diminishment of previous choice influence). The probability of choosing one side or the other was calculated using a softmax function, with the weighted sum of these influences as input (the right plot shows the influence of the inverse softmax temperature parameter: at higher values, the decision is more deterministic).

A computational model of decision-making was applied to the decision behaviour of each subject, with the specific model being chosen from among eleven candidate models based on model comparison (see SI). The model consisted of two influences on the decision to choose the left or right side (Figure 2). The first influence was a decaying working memory trace,  $m$ , of where the food was hidden, modelled as an exponential decay function according to the delay on trial  $t$ ,  $d_t$ :

$$m_t = w_1 S_t e^{-\lambda_1 d_t}$$

where  $w_1$  is the weight of this factor when the delay is 0,  $S_t$  is the side that food was hidden on in trial  $t$  (left = -1, right = 1), and  $\lambda_1$  is the working memory decay rate. The second influence was that of the previous two choices,  $p$ , modelled as an exponential decay function according to the inter-trial interval before trial  $t$ ,  $i_t$ :

$$p_t = w_2 (R_{t-1} e^{-\lambda_2 (i_t + d_t)} + R_{t-2} e^{-\lambda_2 (i_{t-1} + d_{t-1} + i_t + d_t)})$$

where,  $w_2$  is the weight of this factor when the inter-trial interval and delay is 0,  $R_{t-1}$  is the response made on the previous trial (left = -1, right = 1), and  $\lambda_2$  is the decay rate. Positive values of  $w_2$  therefore represent a tendency to repeat the previous choice, whereas negative values represent a tendency to suppress the previous choice, via different degrees of inhibitory control.

The decision variable,  $z$ , was computed as the sum of these two factors,  $m$  and  $p$ , with negative values representing a tendency to choose the left side, and positive values representing a tendency to choose the right side. The decision variable was then transformed into the probability of choosing the right side on trial  $t$ :

$$P(R_t = 1) = \frac{1}{1 + e^{-\beta z_t}}$$

The inverse softmax temperature,  $\beta$ , controls the slope of the softmax function, thereby determining the sensitivity of the choice probability to the decision variable,  $z$ . This parameter is referred to as "choice stochasticity." The model was fit separately to each subject's choice behaviour using maximum log-likelihood estimation in Matlab (v R2018a). To avoid local maxima, a grid search of all parameter values was utilized to initialize the model parameters prior to fitting. The weight of the working memory factor,  $w_1$ , was restricted to the range of [0, 1], while the weight of the choice history factor,  $w_2$ , was restricted to the range of [-1, 1] in order to detect both a tendency to inhibit or repeat the previous choice, thus reflecting different degrees of inhibitory control. The decay rate parameters,  $\lambda_1$  and  $\lambda_2$ , and the inverse softmax temperature,  $\beta$ , were constrained to the range of [0,10].

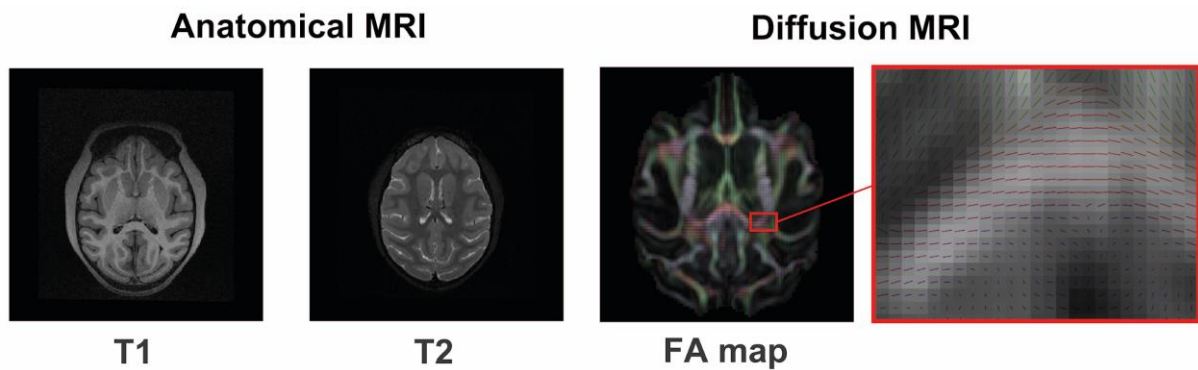
Therefore, five model parameters were available for subsequent analysis:  $w_1$  (the weight of the working memory factor when the delay is 0),  $\lambda_1$  (decaying working memory trace of the food location),  $w_2$  (the weight of the choice factor when the inter-trial interval and delay is 0),  $\lambda_2$  (decaying trace of the previous choice), and  $\beta$  (choice stochasticity).

### ***MRI acquisition***

To investigate changes in brain anatomy and both structural and functional connectivity, magnetic resonance imaging (MRI) data were collected at each project time-point (2.5, 3.5, and 5 years) using a 3T Siemens Prisma MR scanner. The subjects were separated from their social group for a total of approximately 5 hours to undergo the scanning

process. This time period included 45 minutes for preparation, including anaesthesia induction, intubation, and positioning in the scanner, 3 hours of active scanning, and 1 hour of post-anaesthesia recovery. During the scan, the subjects were positioned in a supine position and anaesthetized with isoflurane (1.5%/2% isoflurane, intubation). A stereotaxic frame was employed to secure the head and prevent movement in order to mitigate motion artefacts. A vitamin E capsule was placed on the right temple to serve as a marker for the right brain hemisphere. Alphaxalone was administered for anaesthesia induction, and NaCl was administered intravenously for hydration during the scan. We used local anaesthetic cream (Anesederm) in the external ears conduct prior the installation of the macaque in the stereotaxic frame. The subjects were also placed under an MRI-compatible heating blanket to maintain body temperature. Physiological measures such as heart rate, temperature, and blood oxygenation were continuously monitored and maintained in accordance with veterinary protocols throughout the scan. Upon completion of the scan and full recovery from anaesthesia, the subjects were returned to their social group.

High resolution anatomical MRI (T1/T2) scans were first obtained: MPRAGE T1-weighted images, 0.5mm isotropic, a bandwidth of 250 Hz, a TR of 3000 ms, a TE of 3.62 ms, a TI of 1100 ms, a flip angle of 8° and 144 cross-sections, and SPACE T2-weighted images with a spatial resolution of 0.5mm isotropic, a bandwidth of 710 Hz, a TR of 3000 ms, a TE of 366 ms, a flip angle of 120° and 144 cross-sections (Figure 3). High resolution diffusion MRI scans were then also acquired to investigate differences in brain microstructure: custom pulse sequence based on a segmented 3-dimensional EPI sampling of Fourier space with the following parameters; diffusion weighted images (b-value of 1000 s/mm<sup>2</sup>), 46 directions diffusion gradient encoding with two B0, a spatial resolution of 0.8 mm isotropic, a bandwidth of 776 Hz, a TR of 750 ms, a TE of 71 ms, 4 segments, a FOV of 105x125x56 mm<sup>3</sup> and an acquisition time of 60 minutes (Tounekti et al., 2018) (Figure 3). Scans were acquired successfully from all subjects at both time-points.



**Figure 3.** Examples of raw MRI images from a macaque monkey. The first two images are examples of different structural scans (T1, T2); the third is based on a diffusion MRI scan and shows a fractional anisotropy (FA) color map, displaying the diffusivity vector  $V_1$  (principal direction vector) for each voxel (red represents left-right oriented fibers; blue represents dorsal-ventral oriented fibers; green represents anterior-posterior oriented fibers); the fourth image depicts a close-up view of the FA map.

## ***MRI pre-processing***

### **Anatomical**

The aim of the structural data analysis in this study was to extract and analyse morphometric features such as cortical thickness and volumes. The steps involved in this analysis are similar to the Human Connectome Project pipeline. First, brain extraction was performed using BET (Jenkinson et al., 2002). The T2w and T1w images were then registered and aligned to MNI space to create a native volume space. The resolution was lowered from 0.5 to 1 mm before using FreeSurfer to generate a segmentation of the three brain tissues (white matter, grey matter, and subcortical matter) and create brain surfaces (white matter, pial matter, and mid matter). Finally, the volumes and surfaces were rescaled back to the initial native resolution. Using FreeSurfer and Connectome Workbench anatomical white and pial 32k vertex surfaces were created for all the subjects both in their native space and in MNI nonlinear space. These surfaces were useful for brain cortical parcellation and tissue segmentation and the calculation of cortical thickness. The atlas Markov132 labels were projected onto the brain surfaces (Markov et al., 2014), which were aligned to the MNI nonlinear space. The cortical thickness values in each region of interest (ROI) were then extracted by calculating the mean of the cortical thickness at every vertex within the ROI. This method enabled analysis of morphometric features, specifically here, cortical thickness, within specific regions of the brain. We focused on specific areas corresponding to broader



functional regions of the PFC. The areas 9/46d, 9/46v, 46d, 46v corresponds to dlPFC; the areas 44, 45a, 45b, correspond to vlPFC (see Petrides, 2000, 2002, 2005; Petrides et al., 2012).

### **DTI TBSS**

The diffusion weighted images (DWIs) underwent correction for movement and inhomogeneity distortions, as well as eddy current effects, utilizing FSL's topup and eddy algorithms (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; Woolrich et al., 2009). The DTI maps were computed at the original resolution, and a study-specific template was generated at a higher resolution of 0.4 mm isotropic, through the use of the optimal template construction algorithm in ANTS (Avants et al., 2014). Subsequently, an affine registration of the fractional anisotropy (FA) maps of all subjects was performed onto the study template, resulting in transformation matrices that were employed to upscale the native DTI volumes to the resolution of the template. The decision to upscale was based on a comparison of the Tract-Based Spatial Statistics (TBSS) FA skeletons at both resolutions, with the 0.4 mm resolution resulting in more continuous FA skeletons and a maximum representation of white matter fibers. TBSS, a tool within FSL, enables a voxel-wise statistical approach while mitigating registration bias and multiple comparison issues by identifying the centre of white matter bundles. For increased precision, TBSS non-linear scalar registration was replaced with a tensor registration using DTI-TK to the study-specific template (Zhang et al., 2007). Using the TBSS analysis, the impact of early psychosocial adversity on brain microstructure was studied by investigating the effects of rearing group on axial diffusivity (AD), radial diffusivity (RD), and FA.

### **DTI ROIs**

Diffusion parameters were computed for major brain fiber tracts. In order to obtain more accurate measurements of the DTI parameters in the white matter regions of interest, the extraction of these values was performed on the white matter skeletons generated by TBSS. In fact, the values of the skeletons correspond to the DTI values projected at the center of the bundles and are less impacted by the registration bias. To accomplish this, the ONPRC18 multimodal macaque atlas (Weiss et al., 2021) was intersected with the skeleton masks. Then, for each region of the skeleton conventional DTI methods were used to calculate the mean values of FA, which represents the degree of directionality of random water diffusion, RD, which represents the diffusion of water perpendicular to axonal fibers, and AD, which

represents the diffusion of water parallel to axonal fibers. Higher FA is often interpreted to reflect greater white matter integrity, with the other metrics reflecting other measures and being used to calculate FA. FA is a widely used imaging metric that quantifies the degree of restriction in the direction of water molecule diffusion, and is elevated in white matter tracts that are tightly bundled and organized (Basser, 1995; Beaulieu, 2002; Sen & Basser, 2005). Although FA is highly sensitive to microstructural changes in white matter, it is less sensitive to the type of change. For example, lower FA could indicate either more diffusely organized white matter, lower axonal density, or reductions in myelination. RD and AD, reflect different properties of white matter microstructure (Schmithorst & Yuan, 2010). RD represents the amount of diffusivity that occurs perpendicular to the length of axons and is negatively correlated with myelination levels, reflecting developmental changes in myelination. AD represents the amount of diffusivity that occurs parallel to the length of axons and increases with maturational changes in development, potentially reflecting increased axonal organization and projection. In the current study, the primary analyses were based on FA values. All significant results involving FA in DTI ROIs were also followed up by examining differences in AD and RD in order to probe what may be driving differences in FA (reported in the SI).

### ***Data analysis***

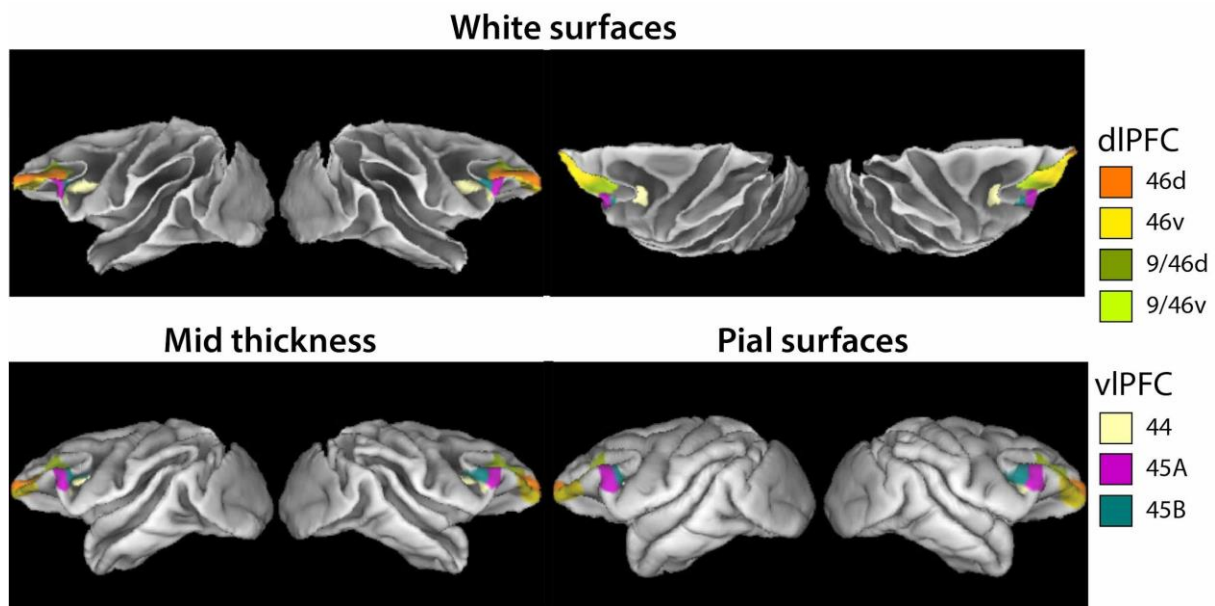
Descriptive statistics for each of the brain measures analysed below are presented in Table S1 of the SI.

### **Executive function**

To compare performance on the original 'A-not-B' task between the two rearing groups over time, we computed a cumulative score (the sum of successful change trial delays divided by the number of total trials completed) for each subject at each assessment time-point. For the cumulative score, we conducted a linear mixed model with group, time-point, and their interaction included as fixed effects, and subject-specific random intercepts. The computational model was fitted separately for each subject at each assessment time-point. To compare the fitted model parameters between the two rearing groups across time, we used linear mixed models with group, time-point, and their interactions included as fixed effects, and subject-specific random intercepts. See Chapter 3 of this thesis for more details on the behavioural analyses.

## Cortical thickness

We then examined differences in cortical thickness in our *a priori* ROIs: the dIPFC, including areas 9/46d, 9/46v, 46d, 46v, and the vIPFC, including areas 44, 45A, 45B (Figure 4). We used a mixed-model approach for analysis, with group (mother-reared/peer-reared), time-point (3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. For each area, right and left hemisphere analyses were run separately. Sex was controlled for in all analyses.



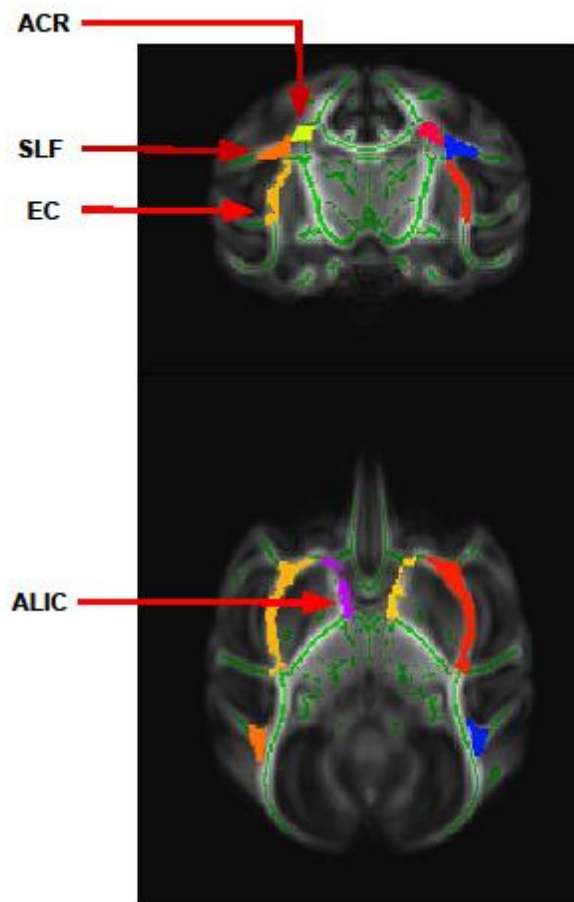
**Figure 4.** ROIs used for analyses of PFC cortical thickness. The different colours represent the different ROIs in dIPFC and vIPFC. These images show the ROIs in different layers of cortex to give a more complete view.

## White matter microstructure (TBSS)

To investigate differences between groups in white matter microstructure over the whole brain without specifying *a priori* regions of interest, we used a tract-based spatial statistics (TBSS) approach. Using the Randomise tool of FSL, a non-parametric t-test with 10000 permutations and threshold-free cluster enhancement was performed to compare white matter microstructure between the two rearing groups. This was done for each of the three assessment time-points and with all time-points combined. The results were corrected using family-wise error correction to avoid false positives generated due to a multiple comparison problem. The results were considered significant at  $p < 0.05$ . Sex was controlled for in all analyses.

### White matter microstructure (ROIs)

We then examined differences in white matter integrity in our *a priori* ROIs: the SLF, i.e. fronto-parietal circuitry linked to EF; and the anterior corona radiata (ACR), anterior limb of internal capsule (ALIC), and external capsule (EC), i.e. fronto-striatal circuitry linked to EF (Figure 5). We used a mixed-model approach for analysis, with group (mother-reared/peer-reared), time-point (3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. Separate analyses were run for each tract in each hemisphere. Sex was controlled for in all analyses.



**Figure 5.** Coronal and axial views of the study template with FA skeleton (green) and symmetrical regions of the ONPCR18 atlas overlaid. ROIs are highlighted as follows: anterior corona radiata (ACR: left hemisphere – yellow; right hemisphere – red); superior longitudinal fasciculus (SLF: left hemisphere – orange; right hemisphere – blue); external capsule (EC: left hemisphere – light orange; right hemisphere – light red); and anterior limb of the interior capsule (ALIC: left hemisphere – purple; right hemisphere – dark yellow).

### **Relationships between cortical thickness in PFC regions and EF**

We also investigated the relationship between general EF performance (cumulative score), as well as the working memory ( $w_1, \lambda_1$ ), inhibitory control ( $w_2, \lambda_2$ ), and choice stochasticity ( $\beta$ ) parameters of the computational model, and cortical thickness of dlPFC, and vlPFC both concurrently and prospectively. Separate models were run for each ROI and hemisphere. As a number of analyses were run predicting the same outcome (see below), our Bonferroni-adjusted alpha level for significance was set to  $p = 0.0036$  (i.e.  $p = 0.05/14$ ; left and right hemisphere, 7 regions). Descriptive statistics for each variable are shown in Table S1 in the SI.

#### ***Concurrent statistical analyses***

To examine concurrent relationships between cortical thickness and EF, a mixed modelling framework was adopted. For cumulative score,  $w_1$ ,  $w_2$ ,  $\lambda_2$ , and  $\beta$ , we used linear mixed models with cortical thickness, group (mother-reared/peer-reared), time-point (3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. For  $\lambda_1$  (which was binarized due to the variable distributed around 0 and 1), we used a generalized linear mixed model with a binomial distribution, with logit as the link function, and with cortical thickness, group, time-point, and their interactions included as fixed effects, and subject-specific random intercepts.

#### ***Prospective statistical analyses***

To examine how cortical thickness measures at 3.5 years may prospectively predict EF at 5 years, we also ran a number of regression analyses. For cumulative score,  $w_1$ ,  $w_2$ ,  $\lambda_2$ , and  $\beta$  at 5 years, we used linear regressions with cortical thickness at 3.5 years, group (mother-reared/peer-reared), and their interactions as fixed effects. For  $\lambda_1$  at 5 years, we used a generalized linear regression with a binomial distribution, with logit as the link function, and with cortical thickness at 3.5 years, group, and their interactions included as fixed effects.

### **Relationships between structural connectivity in fronto-parietal and fronto-striatal circuits and EF**

Finally, we investigated the relationships between general EF performance (cumulative score), as well as the working memory ( $w_1, \lambda_1$ ), inhibitory control ( $w_2, \lambda_2$ ), and choice

stochasticity ( $\beta$ ) parameters of the computational model, and white matter integrity of the SLF, ACR, ALIC, and EC, both concurrently and prospectively. Separate models were run for each ROI and hemisphere. As a number of analyses were run predicting the same outcome (see below), our Bonferroni-adjusted alpha level for significance was set to  $p = 0.006$  (i.e.  $p = 0.05/8$ ; left and right hemisphere, four tracts). Descriptive statistics for each variable are shown in Table S1 in the SI.

### ***Concurrent statistical analyses***

To examine concurrent relationships between DTI measures and EF, a mixed modelling framework was adopted. For cumulative score,  $w_1$ ,  $w_2$ ,  $\lambda_2$ , and  $\beta$ , we used linear mixed models with DTI, group (mother-reared/peer-reared), time-point (3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. For  $\lambda_1$  (which was binarized), we used a generalized linear mixed model with a binomial distribution, with logit as the link function, and with DTI, group, time-point, and their interactions included as fixed effects, and subject-specific random intercepts.

### ***Prospective statistical analyses***

To examine how DTI measures at 3.5 years may predict EF prospectively at 5 years, we also ran a number of regression analyses. For cumulative score,  $w_1$ ,  $w_2$ ,  $\lambda_2$ , and  $\beta$  at 5 years, we used linear regressions with DTI at 3.5 years, group (mother-reared/peer-reared), and their interactions as fixed effects. For  $\lambda_1$  at 5 years, we used a generalized linear regression with DTI at 3.5 years, group, and their interactions included as fixed effects.

R v4.2.1 was utilized to conduct all analyses presented here involving cortical and white matter ROIs (see SI for package information).  $P$ -values for fixed effects and interactions were obtained using Type III F tests for linear models, and Type III Wald  $\chi^2$  tests for generalized linear models. Sex was controlled for in all analyses, and presence of influential cases was checked for and data points with a Cook's distance higher than 1 were removed.

## Results

### ***General EF, working memory, and inhibitory control***

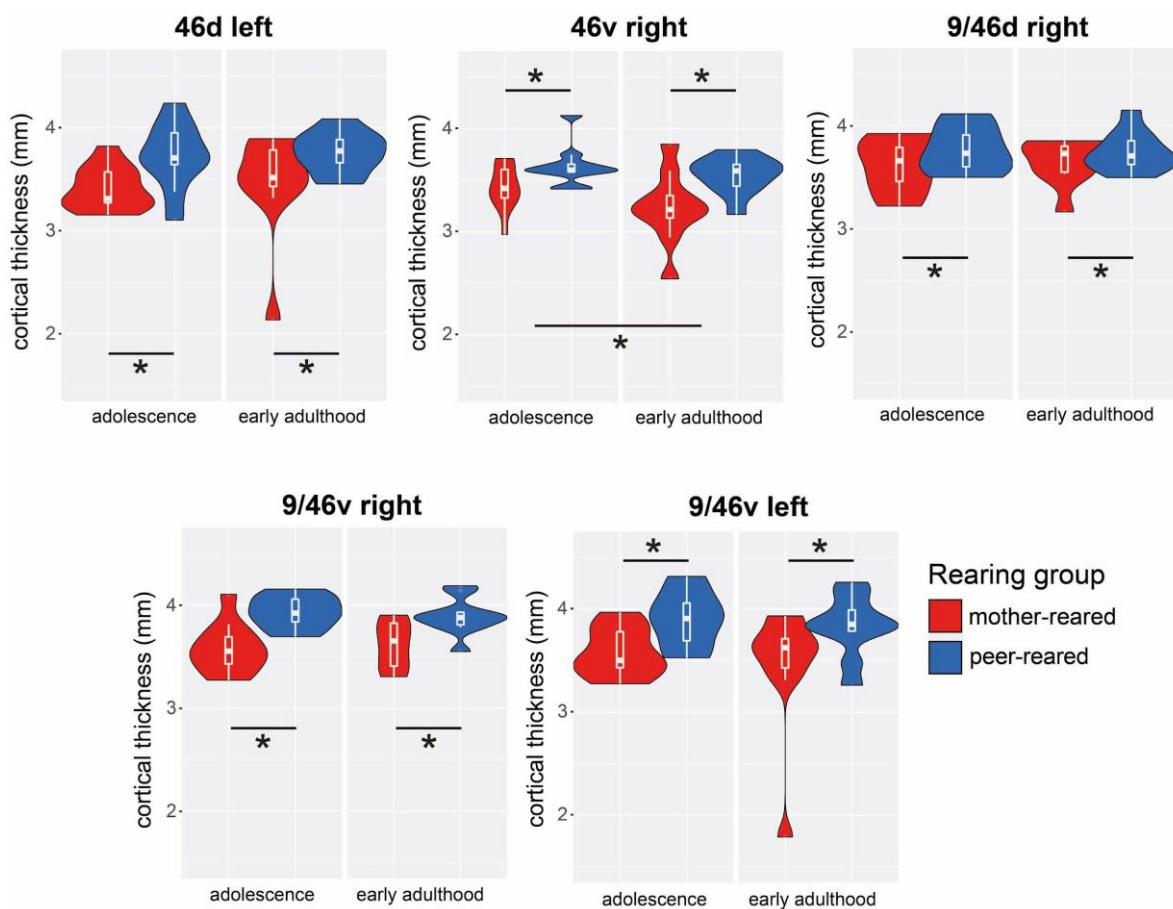
The following is a summary of the results from Massera et al., (*in press*) (Chapter 3). We first aimed to investigate potential variations in task performance between the two rearing groups and time-points by comparing the cumulative score from the 'A-not-B' task. The results show that the mother-reared group performed better than the peer-reared group, with a significant main effect of group revealed [ $F(1) = 12.643, p < 0.01$ ]. There were no significant effects of time-point or the interaction between group and time-point. We then sought to investigate the cognitive mechanisms that underlie the observed performance differences between the two groups via comparison of the fitted computational model parameters. Results revealed a significant main effect of group on working memory decay ( $\lambda_1$ ) [ $F(1) = 7.008, p = 0.014$ ], with the peer-reared group exhibiting a faster rate of decay compared to the mother-reared group. No significant effects of time-point or group by time-point interaction were found, nor were there any significant differences in the weight of working memory parameter ( $w_1$ ). Additionally, no main effects of group or time-point were observed on the weight of the choice history parameter ( $w_2$ ). However, a significant interaction between group and time-point was detected [ $F(1) = 7.159, p = 0.021$ ], with  $w_2$  decreasing from time-point 1 to time-point 2 in the mother-reared group, and increasing in the peer-reared group. However, we did not find a significant difference between the two group and between time-points in follow-up analyses. No main effects or interactions were found for choice history decay rate ( $\lambda_2$ ), or choice stochasticity ( $\theta$ ). See Chapter 3, Figures 4- 6.

Therefore, peer-reared animals were found to demonstrate worse general EF, performing worse on the 'A-not-B' task at both time-points compared to mother-reared. This poor performance appears related to both problems in working memory at 3.5 and 5 years, and inhibitory control at 5 years. See SI for descriptive measures (Table S1).

### ***Groups differences in dlPFC and vlPFC thickness associated with EF***

We then wanted to investigate the effects of early psychosocial deprivation on the development of two specific prefrontal regions important for EF (dlPFC, and vlPFC) across adolescence into adulthood. In the text the significant cortical thickness main effects or interactions are reported (see also Table S2 in the SI).

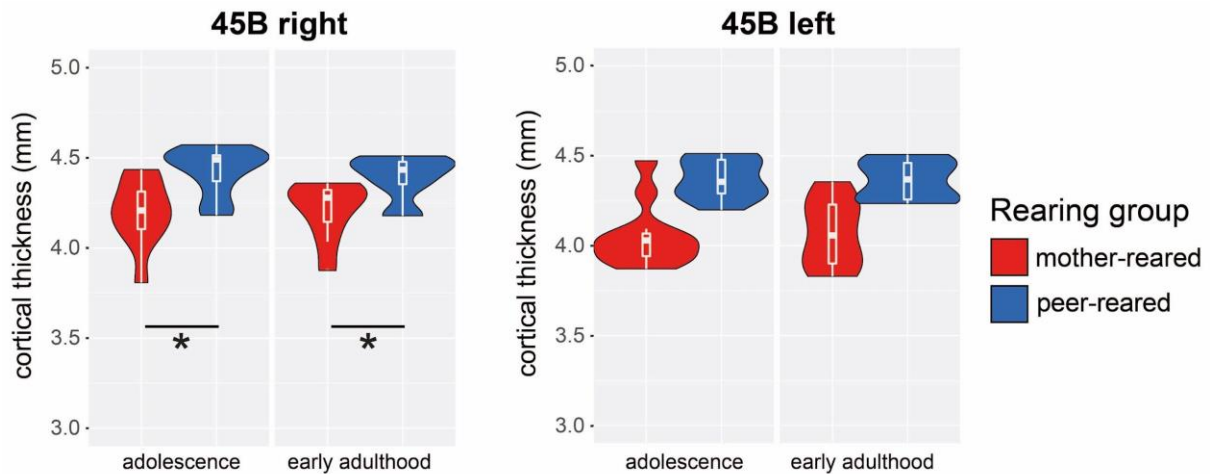
For dlPFC, a significant main effect of group was found in several areas (Figure 6). The peer-reared group had thicker cortex in the left 46d area [ $\chi^2(1) = 7.642, p = 0.006$ ], in the right 46v area [ $\chi^2(1) = 3.96, p = 0.047$ ], in the right 9/46d area [ $\chi^2(1) = 4.263, p = 0.039$ ], and in both the right and left 9/46v areas [right,  $\chi^2(1) = 4.884, p = 0.027$ ; left,  $\chi^2(1) = 5.54, p = 0.019$ ]. In addition, we also found an effect of year in the right 46v area [ $\chi^2(1) = 8.301, p = 0.004$ ], with thinner cortex at 5 years in both groups. No other significant main effects or interactions were found in dlPFC.



**Figure 6.** Group differences in dlPFC cortical thickness in the different ROIs. Across time, greater cortical thickness was found in the peer-reared (blue) versus mother-reared (red) group in the left 46d, the right 46v, the right 9/46d, and the right and left 9/46v areas. Only in the right 46v we found thinner cortex in early adulthood compared to adolescence in both groups. Significant effects are denoted by \*. Violin plots represent the density of the variable, while box-plots represent summary statistics, with error bars reflecting  $\pm$  SE.

For vlPFC, a significant main effect of group was found in both the right and the left 45B areas [right,  $\chi^2(1) = 10.847, p < 0.001$ ; left,  $\chi^2(1) = 22.1, p < 0.001$ ], with thicker cortex in the peer-reared group compared to the mother-reared group (Figure 7). No other significant main effects or interactions were found in vlPFC.

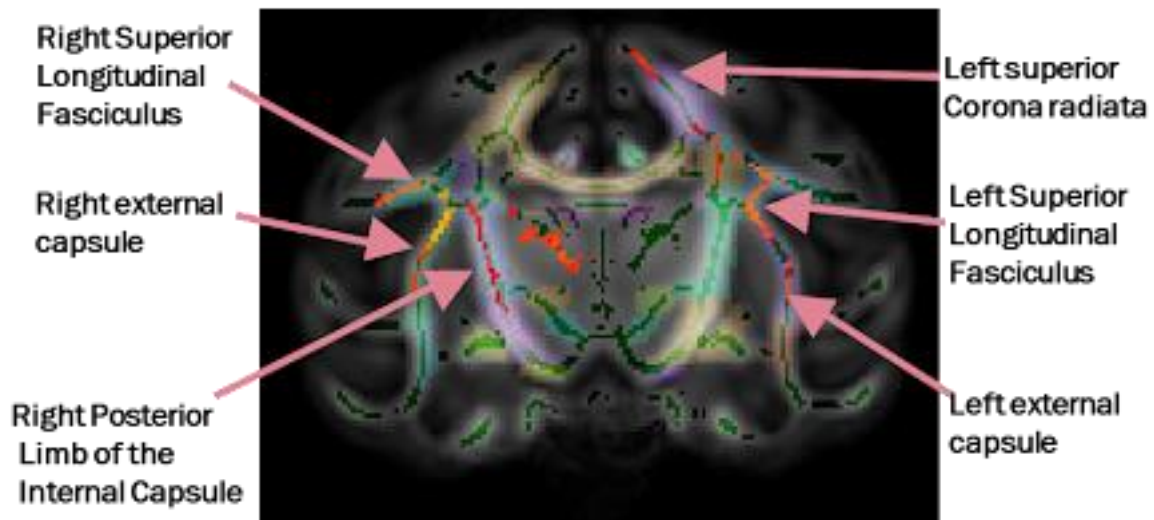




**Figure 7.** Group differences in vIPFC cortical thickness in the different ROIs. Across time, greater cortical thickness was found in the peer-reared (blue) versus mother-reared (red) group in the right and left 45B areas. Significant effects are denoted by \*. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting +/- SE.

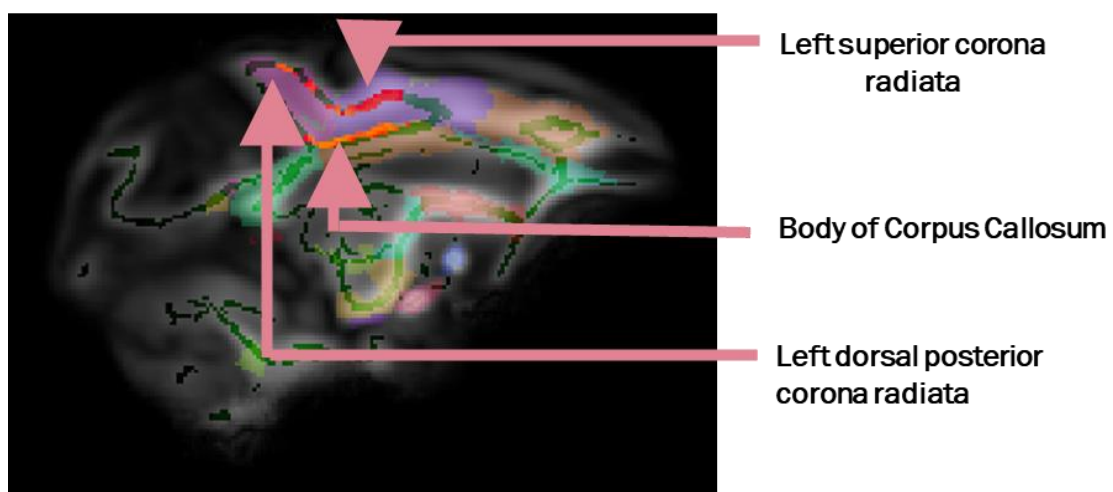
### ***Differences in whole-brain white matter between groups***

We then examined the effects of early social deprivation on white-matter integrity overall. We compared whole brain white-matter integrity between the two groups using TBSS at three time-points separately (2.5, 3.5, and 5 years) and with the three years pooled together. We did not find any significant results between the two groups in the analyses at the three time-points separately. In addition, the results show no significant difference in FA between the two groups with the three years pooled together. However, we found a significant difference between the two groups in RD (Figure 8) in the right and left SLF, right and left EC, left superior corona radiata, and right posterior limb of the internal capsule, with RD greater in the mother-reared versus peer-reared group (all clusters  $p < 0.05$ ).



**Figure 8.** *TBSS analysis results (RD).* Main effects of group. Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Red/yellow voxels represent the statistically significant clusters (thresholded at  $p < 0.05$ ) where mother-reared animals had significantly higher RD than the nursery-reared ones. The ONPRC18 atlas is overlaid on the image to locate the regions where the clusters belong.

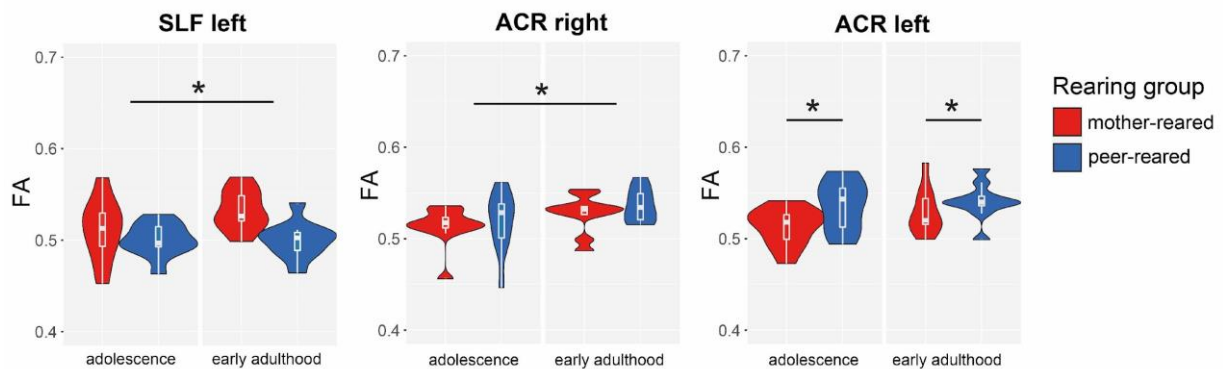
We also found significant differences between the two groups in AD (Figure 9), with mother-reared having higher AD in the left superior corona radiata, body of corpus callosum, and left dorsal posterior corona radiata (all  $p < 0.05$ ).



**Figure 9.** *TBSS analysis results (AD).* Main effects of group. Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Red/yellow voxels represent the statistically significant clusters (thresholded at  $p < 0.05$ ) where mother-reared animals had significantly higher AD than the nursery-reared ones. The ONPRC18 atlas is overlaid on the image to locate the regions where the clusters belong.

## Group differences in white matter tracts associated with EF

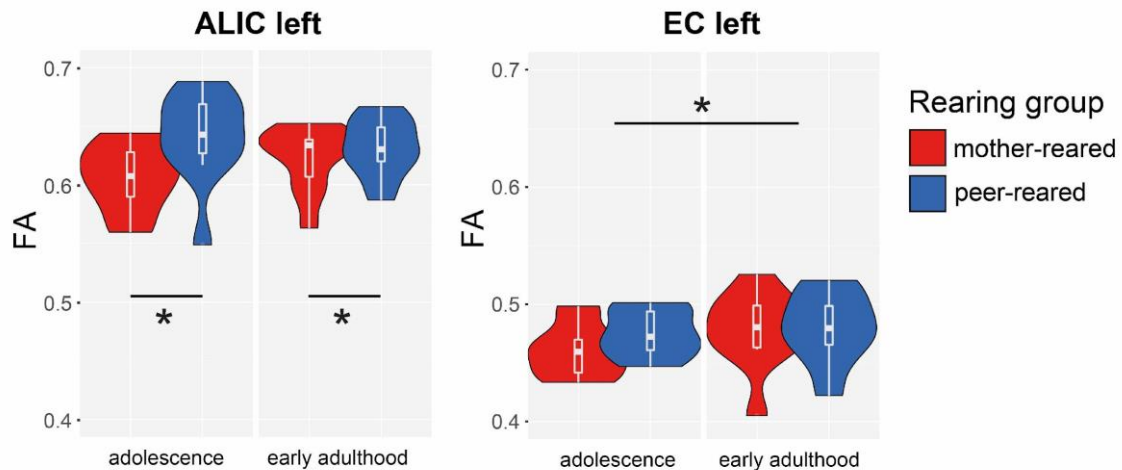
We then investigated the effects of early psychosocial deprivation on the development of four specific white-matter tracts important for EF (SLF, ALIC, ACR, EC) across adolescence into adulthood. In the text the significant cortical thickness main effects or interactions are reported (see also Table S2 in the SI).



**Figure 10.** Group differences in FA in the SLF and ACR white matter tracts. Across time, greater white-matter integrity was found in the peer-reared (blue) versus mother-reared (red) group in the left anterior corona radiata (ACR). In both groups, greater white-matter integrity was found in early adulthood compared to adolescence in the left superior longitudinal fasciculus (SLF), and in the right ACR. Significant effects are denoted by \*. Violin plots represent the density of the variable, while boxplot represent summary statistics, with error bars reflecting +/- SE.

For SLF, a significant main effect of time-point was observed in the left hemisphere [ $\chi^2(1) = 5.712, p = 0.017$ ]. Specifically, there was higher FA at 5 years compared to 3.5 years (Figure 10). However, no significant effect of group or group by time-point interaction was found in the left SLF, and no significant results were observed in the right FA SLF.

For ACR, we found a significant main effect of year in the right hemisphere [ $\chi^2(1) = 4.647, p = 0.031$ ], with higher FA at 5 years compared to 3.5 years. We did not find a significant effect of group or group by time-point interaction in right ACR. In contrast, in the left ACR, we identified a significant main effect of group [ $\chi^2(1) = 4.632, p = 0.031$ ], with higher FA in the peer-reared group compared to the mother-reared group. In the left ACR we also detected a trend for time-point [ $\chi^2(1) = 3.638, p = 0.056$ ], with higher FA at 5 years compared to 3.5 years. No significant group by time-point interaction for FA was detected in the left ACR. These results are illustrated in Figure 10.



**Figure 11.** Group differences in FA in the ALIC and EC white matter tracts. Across time, greater white-matter integrity was found in the peer-reared (blue) versus mother-reared (red) group in the left anterior limb of internal capsule (ALIC). In both groups, greater white-matter integrity was found in early adulthood compared to adolescence in the left external capsule (EC). Significant effects are denoted by \*. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting +/- SE.

For ALIC, we found a significant main effect of group in the left hemisphere [ $\chi^2(1) = 8.199, p = 0.004$ ], with higher values of FA in peer-reared animals compared to mother-reared animals. There was no effect of time-point or group by time-point interaction in the left hemisphere for FA. Furthermore, no significant results were obtained in the right ALIC. These results are illustrated in Figure 11.

For EC, we identified a significant main effect of time-point on FA in the left hemisphere [ $\chi^2(1) = 4.970, p = 0.026$ ], with higher values at 5 years compared to 3.5 years (Figure 11). No other significant relationships were found in the right and left EC for FA.

## ***Relationships between cortical thickness in PFC regions and EF***

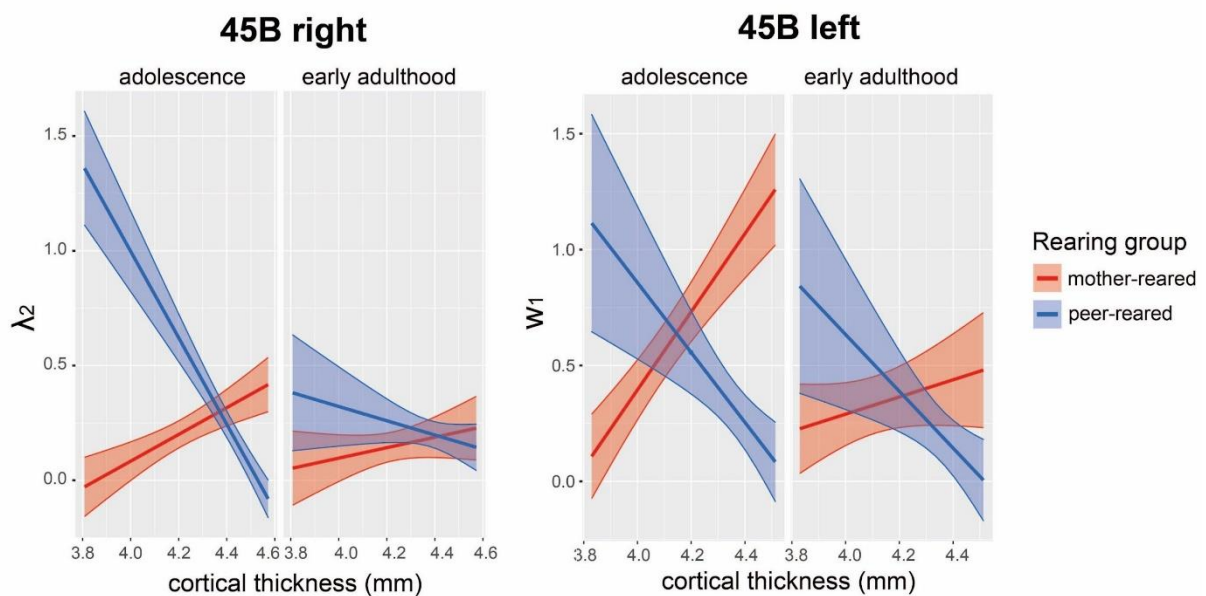
### **Concurrent cortical thickness ROI-EF relationships**

In order to determine whether differences in EF between the two rearing groups were associated with concurrent differences in the cortical thickness of relevant neural circuitry over time, we examined the relationship between cortical thickness in two prefrontal areas (dlPFC, vlPFC) and EF as measured via the cumulative score and fitted model parameters. In the text the significant cortical thickness main effects or interactions are reported, while all the other effects and interactions reported in Table S3 in the SI.

For dlPFC, a number of significant interactions with cortical thickness were revealed. For the analysis predicting  $w_1$ , in area 9/46d we found a significant interaction between cortical thickness, and time-point in the left hemisphere [ $\chi^2(1) = 10.909, p = <0.001$ ]. Specifically, at 5 years, thicker cortex was related to lower  $w_1$  (i.e. worse working memory), compared to 3.5 years [ $t(1) = 2.771, p = 0.0143$ ]. For  $w_1$ , we also found a significant interaction in area 9/46v between cortical thickness and time-point in the right hemisphere [ $\chi^2(1) = 11.285, p < 0.001$ ]. However, the follow-up analyses were not significant. For  $\beta$ , we found a significant interaction in area 46d between cortical thickness, and group in the right hemisphere [ $\chi^2(1) = 8.657, p = 0.003$ ]. Specifically, the mother-reared group differed from the peer-reared group [ $t(1) = 2.352, p = 0.0257$ ], but no other significant follow-ups were found.

For vlPFC, a number of significant interactions with cortical thickness were revealed. For cumulative score, we found a significant interaction in area 44 between cortical thickness, and time-point in the right hemisphere [ $\chi^2(1) = 8.61, p = 0.003$ ]. However, the follow-up analyses were not significant. For cumulative score we also found a significant interaction in area 45B between cortical thickness and time-point in the right hemisphere [ $\chi^2(1) = 18.735, p < 0.001$ ], with the cortical thickness – cumulative score relationship changing from 3.5 years to 5 years [ $t(1) = 2.896, p = 0.01$ ], but no other significant follow-ups were found. For the analysis predicting  $w_1$ , we found a significant interaction in area 45B between cortical thickness and group [ $\chi^2(1) = 9.978, p = 0.001$ ], and between cortical thickness and year in the left hemisphere [ $\chi^2(1) = 9.031, p = 0.002$ ] (Figure 12). The follow-up tests for the group by time-point interaction were not significant, but for the mother-reared animals, thicker cortex in area 45B was related to higher  $w_1$  (i.e. better working memory) [ $t(1) = 2.043, p = 0.05$ ], compared to the peer-reared group [ $t(1) = 2.445, p = 0.0208$ ]. For the analysis predicting  $\lambda_1$ , we found a significant interaction in area 45A between cortical thickness, time-point, and group in the right hemisphere [ $\chi^2(1) = 9.251, p < 0.001$ ]. At 3.5 years for the mother-reared group, thicker cortex was related to lower  $\lambda_1$  (i.e. slower working memory decay / better working memory) [ $t(1) = -2.765, p = 0.006$ ], compared to the peer-reared group [ $t(1) = -2.778, p = 0.005$ ], and to 5 years [ $t(1) = -2.983, p = 0.003$ ]. For the analysis predicting  $\lambda_2$ , we found a significant interaction in area 45B between cortical thickness, time-point, and group in the right hemisphere [ $\chi^2(1) = 8.517, p = 0.003$ ] (Figure 12). Specifically, at 3.5 years for the peer-reared group, thicker cortex was related to lower  $\lambda_2$  (i.e. slower decay/ worse inhibitory

control) [ $t(1) = -4.544, p < 0.001$ ], compared to the mother-reared group [ $t(1) = 4.841, p < 0.001$ ], and to 5 years [ $t(1) = -2.866, p = 0.01$ ]. For the analyses of  $\beta$ , we found a significant interaction between cortical thickness, group, and time-point in area 45A in the left hemisphere [ $\chi^2(1) = 9.117, p = 0.002$ ]. That is, in the peer-reared group at 3.5 years, thicker cortex was related to a lower  $\beta$  (i.e. more random choices) [ $t(1) = -2.193, p = 0.036$ ], compared to 5 years [ $t(1) = -2.131, p = 0.047$ ], and differing from the mother-reared group at 3.5 years [ $t(1) = 2.609, p = 0.014$ ]. Additionally, the relationship between cortical thickness and  $\beta$  in the mother-reared group changed from 3.5 years to 5 years [ $t(1) = 2.169, p = 0.047$ ], but no other significant follow-ups were found. For  $\beta$ , an interaction between cortical thickness and group was found in area 45B in the right hemisphere [ $\chi^2(1) = 8.596, p = 0.003$ ], with thicker cortex related to lower  $\beta$  (i.e. more random choices) in the peer-reared group [ $t(1) = -2.360, p = 0.025$ ].



**Figure 12.** *vIPFC thickness and parameters interaction.* Greater cortical thickness predicted lower  $\lambda_2$  (i.e. slower decay/ worse inhibitory control) in the peer-reared (blue) versus mother-reared (red) group in right area 45B, during adolescence but not in early adulthood. Thicker cortex in left area 45B predicted higher  $w_1$  (i.e. better working memory) in mother-reared group compared to peer-reared group across adolescence into early adulthood. Error bars represent  $\pm$  SE.

### **Prospective cortical thickness ROI-EF relationships**

We then sought to determine whether cortical thickness in the same prefrontal areas (dlPFC, vlPFC) during adolescence prospectively predicted EF in early adulthood. No significant results were revealed.

### ***Relationships between structural connectivity in fronto-parietal and fronto-striatal circuits and EF***

#### **Concurrent DTI ROI-EF relationships**

In order to determine whether differences in EF between the two rearing groups were associated with concurrent differences in the structural connectivity of relevant neural circuitry over time, we examined the relationship between white matter integrity in four WM tracts (SLF, ACR, ALIC, EC) and EF as measured via the cumulative score and fitted model parameters. In the text the significant DTI main effects or interactions are reported, while all the other effects and interactions reported in Table S3 in SI.

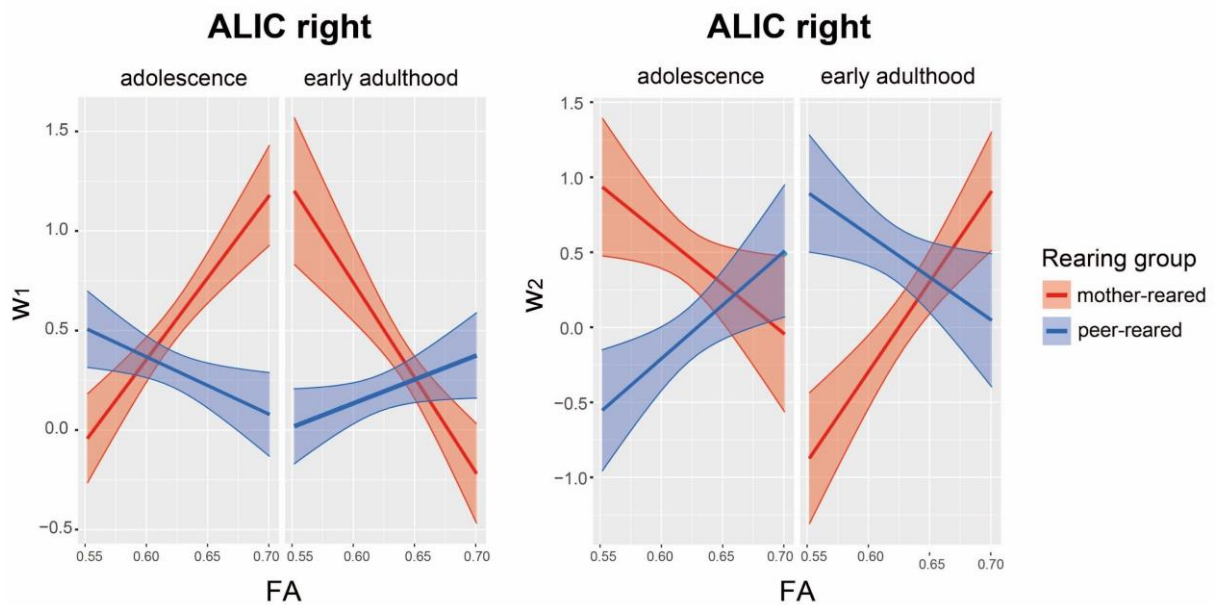
For the SLF, we found a significant interaction between FA and time-point related to cumulative score in the right hemisphere [ $\chi^2(1) = 7.54, p = 0.006$ ]. Specifically, at 3.5 years, higher FA was related to greater cumulative score (i.e. better performance) [ $t(1) = 2.677, p = 0.011$ ], being different from 5 years [ $t(1) = 2.280, p = 0.032$ ]. Additionally, higher FA was related to a greater cumulative score (i.e. better EF performance) in the left hemisphere, with a main effect of FA revealed [ $\chi^2(1) = 16.106, p < 0.001$ ]. We did not find any other significant effects of time-point, group, or interactions for SLF for other outcome variables.

For the ACR, for analyses predicting  $\lambda_1$ , a significant interaction between FA, group, and time-point was revealed in the left hemisphere [ $\chi^2(1) = 2043.796, p < 0.001$ ]. For the mother-reared group at 5 years, higher FA was related to lower  $\lambda_1$  (i.e. slower working memory decay/better working memory) [ $z(1) = -35.237, p < 0.001$ ], compared to the peer-reared group at 5 years [ $z(1) = -35.696, p < 0.001$ ], and to 3.5 years [ $z(1) = 48.370, p < 0.001$ ]. We did not find any other significant effects of time-point, group, or interactions for ACR for other outcome variables.

For the ALIC, a number of significant interactions with FA were revealed. For the analysis predicting  $w_1$ , we found a significant interaction between FA, group, and time-point

in the right hemisphere [ $\chi^2(1) = 15.234, p < 0.001$ ] (Figure 13). That is, in the mother-reared group, higher FA was related to higher  $w_1$  (i.e. better working memory) at 3.5 years [ $t(1) = 2.688, p = 0.011$ ] significantly different from the peer-reared group [ $t(1) = 2.701, p = 0.012$ ], but to a lower  $w_1$  (i.e. worse working memory) at 5 years [ $t(1) = -2.290, p = 0.03$ ] significantly different from the peer-reared group [ $t(1) = -2.444, p = 0.021$ ], and differing between the two time-points [ $t(1) = 3.446, p = 0.002$ ]. Additionally, for the analysis predicting the decay rate of working memory ( $\lambda_1$ ), we also found a significant interaction between FA, group, and time-point in the right hemisphere [ $\chi^2(1) = 2.6082e+07, p < 0.001$ ]. In the mother-reared group, higher FA was related to higher  $\lambda_1$  (i.e. faster working memory decay /worse working memory) at both time-points [3.5 years,  $z(1) = 9850.001, p < 0.001$ ; 5 years,  $z(1) = 2398.029, p < 0.001$ ], with a stronger effect seen at 3.5 years [ $z(1) = 6459.734, p < 0.001$ ]. In the peer-reared group, higher FA was related to lower  $\lambda_1$  (i.e. slower working memory decay / better working memory) at both time-points [3.5 years,  $z(1) = -2835.353, p < 0.001$ ; 5 years,  $z(1) = -2691.382, p < 0.001$ ], with a stronger effect seen at 5 years [ $z(1) = 970.664, p < 0.001$ ]. The relationship between FA and  $\lambda_1$  also differed between the mother-reared and peer-reared groups at both time-points [3.5 years,  $z(1) = 13862.528, p < 0.001$ ; 5 years,  $z(1) = 6205.178, p < 0.001$ ]. Finally, for the analysis of the weight of the choice history factor ( $w_2$ ), a significant interaction between white matter integrity (FA), group, and time-point in the right hemisphere was found [ $\chi^2(1) = 8.134, p = 0.004$ ] (Figure 13). Specifically, higher FA in the mother-reared group was related to higher  $w_2$  (i.e. repeating previous choices more frequently/worse response inhibition) at 5 years [ $t(1) = 2.250, p = 0.031$ ], differing from 3.5 years [ $t(1) = -2.242, p = 0.032$ ], and from the peer-reared group [ $t(1) = 2.332, p = 0.026$ ]. No significant effects of FA were found on the decay rate of choice history ( $\lambda_2$ ), choice stochasticity ( $\theta$ ), or cumulative score.





**Figure 13.** Right anterior limb of internal capsule (ALIC) FA and parameters interactions. Higher FA in the right ALIC was related to higher  $w_1$  (i.e. better working memory) during adolescence, but to a lower  $w_1$  (i.e. worse working memory) in early adulthood in the mother-reared group (red) compared to the peer-reared group (blue). In the right ALIC, higher FA was also related to higher  $w_2$  (i.e. repeating previous choices more frequently/worse response inhibition) in early adulthood in the mother-reared group (red) compared to the peer-reared group (blue). Error bars represent  $\pm$  SE.

For the EC, we found a significant interaction between FA, group, and time-point for the analysis predicting the decay rate of working memory ( $\lambda_1$ ) in both hemispheres [right,  $\chi^2(1) = 120.5388, p < 0.001$ ]; left,  $\chi^2(1) = 2.5229e+10, p < 0.001$ ]. Specifically, in the right EC, higher FA was related to lower  $\lambda_1$  (i.e. slower working memory decay / better working memory) at 5 years in the mother-reared group [ $z(1) = -14.588, p < 0.001$ ], compared to 3.5 years [ $z(1) = 12.970, p < 0.001$ ], and compared to the peer-reared group [ $z(1) = -12.187, p < 0.001$ ]. In the left EC, at 3.5 years, higher FA was also related to higher  $\lambda_1$  (i.e. faster working memory decay/worse working memory) in both groups [mother-reared,  $z(1) = 1261.430, p < 0.001$ ; peer-reared,  $z(1) = 6639.270, p < 0.001$ ], with a stronger effect in the peer-reared group [ $z(1) = -7873.180, p < 0.001$ ]. At 5 years, higher FA was related to lower  $\lambda_1$  (i.e. slower working memory decay / better working memory) in both groups [mother-reared,  $z(1) = -161383.850, p < 0.001$ ; peer-reared,  $z(1) = -24695.320, p < 0.001$ ], with a stronger effect in the mother-reared group [ $z(1) = -129133.570, p < 0.001$ ]. For both rearing groups the FA -  $\lambda_1$  relationship differed between the two time-points [mother-reared,  $z(1) = 207545.560, p < 0.001$ ; peer-reared,  $z(1) = 37728.890, p < 0.001$ ]. We also did not find any interaction between FA and the weight of

working memory ( $w_1$ ), weight of choice history ( $w_2$ ), decay rate of choice history ( $\lambda_2$ ), choice stochasticity ( $\beta$ ), or cumulative score.

### **Prospective DTI-EF relationships**

We then sought to determine whether white matter integrity (FA) in the same four WM tracts (SLF, ALIC, ACR, EC) during adolescence prospectively predicted EF in early adulthood.

For the SLF at 3.5 years, in the models predicating  $w_2$  at 5 years, we found a main effect of FA, with higher FA related to lower  $w_2$  (i.e. repeating fewer previous choices/worse response inhibition) [ $F(1) = 13.296, p = 0.003$ ] in the right hemisphere. Finally, no other main effects of FA or FA, group, time-point interactions were found in any other models.

## **Discussion**

The purpose of this study was to examine how effects of early psychosocial deprivation on macaque executive function (EF) are modulated by structural brain development across adolescence into early adulthood. Using both anatomical and diffusion MRI, we sought to clarify this relationship between EF and specific brain regions and circuitry critical for EF using different metrics of assessment, including gray matter thickness in PFC and white matter microstructure in fronto-parietal and fronto-striatal fiber tracts. Results indicate a functional division in the lateral PFC, with the dlPFC associated with working memory and stochasticity of choice behavior (or ‘randomness’ in decision making), and the vlPFC associated with all EF measures. Differences between rearing groups were found for dlPFC and vlPFC thickness, with differences in vlPFC also predicting differences in EF between rearing groups. Early psychosocial deprivation was also linked to differing developmental trajectories of white matter microstructure in fronto-parietal and fronto-striatal circuits. Both fronto-parietal and most fronto-striatal tracts underwent protracted development across adolescence into adulthood, with increased white matter integrity predicting EF in opposite directions in the peer-reared versus mother-reared group in fronto-striatal circuitry. These findings provide new insights into the longitudinal and long-term effects of early psychosocial deprivation on neurocognitive development in macaques, highlighting the involvement of the vlPFC and

fronto-striatal circuits in the poor EF seen in affected individuals, during the transition between adolescence and adulthood. Additionally, these results offer novel information about the neural bases of general and specific components of executive function across normative macaque development.

### ***Cortical thickness in lateral prefrontal cortex***

Findings regarding cortical thickness in the lateral PFC supported our hypothesis, with thicker cortex found in the peer-reared compared to mother-reared group in both the dlPFC and vlPFC. An effect of age was found only in dlPFC, with thinner cortex in both groups in early adulthood compared to adolescence. These findings are in line with studies on institutionalization in humans, which found greater cortical thickness (including in PFC) in institutionalized adolescents and young adults compared to non-institutionalized individuals (Mackes et al., 2020; Sheridan et al., 2022). This is also in keeping with studies on normative development in terms of cortical thickness in humans and macaques, with thinning seen across adolescence (e.g. Ramirez et al., 2021). Our results also support the idea that, like in humans, the lateral PFC plays an important role in the refinement of EF in macaques across adolescence. More specifically, the dlPFC was linked to working memory in both groups, with thicker cortex predicting worse perceptual salience in working memory (i.e.  $w_1$  – the initial weight of the influence of working memory with no delay) in early adulthood in all animals. The vlPFC was linked to different and overlapping measures of EF, with changes in some of these relationships seen over time, and more differences between rearing groups found. Notably, vlPFC thickness in the right hemisphere predicted general EF differently across time, and better information retrieval/longer-term working memory maintenance (i.e.  $\lambda_1$  – the decay rate of working memory traces) in adolescence in mother-reared group. Conversely, thicker vlPFC in the right hemisphere predicted worse inhibitory control maintenance (i.e.  $\lambda_2$  – the decay rate of the influence of the previous choices) in adolescence and more random decisions (i.e.  $\beta$  – the slope of the softmax decision function) across time in the peer-reared group. Additionally, thicker cortex in the left vlPFC in the mother-reared group predicted both better working memory in terms of perceptual salience across time and predicted decision-making (i.e.  $\beta$ ) across time differently, while in the peer-reared group, thicker cortex in this region predicted more random choices (i.e.  $\beta$ ) during adolescence. We did not find prospective relationships between dlPFC or vlPFC and EF. This may suggest that other brain measures

better predict future EF capacity, such as functional activity, or a combination of factors. To test this, a larger sample size would be needed.

These results concerning cortical thickness partially align with previous research indicating significant contributions of both the dlPFC and vlPFC to working memory and inhibitory control in humans. For example, dlPFC has been associated with domain general executive control functions, cognitive control, and aspects of working memory (Haber et al., 2021; Hertrich et al., 2021; Nejati et al., 2018; Petrides, 2005), while vlPFC has been linked to active valuation, inhibition, rule acquisition, and for the delay phase of working memory tasks (Haber et al., 2021; Nelson & Guyer, 2011). Evidence also suggests that both dlPFC and vlPFC play an important role in working memory and inhibitory control across development (Fiske & Holmboe, 2019). Previous research with macaques suggests that dlPFC is more clearly linked to working memory monitoring and abstract rules, while vlPFC is linked to first-order executive processes such as active selection, comparison, and judgement of stimuli held in shorter-term and longer-term memory (Petrides, 2002; Petrides et al., 2012). Our findings do support the existence of a functional division between dlPFC and vlPFC, with dlPFC being more involved in working memory specifically and choice randomness, and vlPFC related to multiple measures including general EF performance.

To summarise findings in terms of PFC cortical thickness, the peer-reared group had greater thickness in both dlPFC and vlPFC. In dlPFC, thicker cortex predicted better EF in both groups in early adulthood. In vlPFC, thicker cortex predicted worse EF in the peer-reared group, while it predicted better EF in the mother-reared group across time. Notably, while the peer-reared group had thicker cortex in both dlPFC and vlPFC, it also appeared that both groups have greater thickness in vlPFC compared to dlPFC (though we did not test the latter statistically; see SI for descriptive statistics). This could suggest that for vlPFC in mother-reared animals, thicker cortex at the ages examined in the current research reflect normative and beneficial development, enabling the continuation of refinement in EF, and thus increased flexibility and plasticity in terms of subsequent development. In the peer-reared animals, however, greater vlPFC thickness (which was also thicker overall in peer versus mother groups) may have reflected supra-optimal development, with a lack of expected thinning taking place due to accelerated development prior to adolescence, and hence being associated with impaired EF. If dlPFC undergoes less protracted development than vlPFC,

thicker cortex in dlPFC here could reflect delayed or less flexible development in all animals, thus being associated with worse behavioural outcomes but not differently between groups. In fact, evidence suggest that working memory develops largely prior to puberty, as well as associated cortical development (e.g. dlPFC) (Zhou et al., 2016), while inhibitory control and vlPFC undergo a more protracted period of development and plasticity, in both humans and macaques (Sydnor et al., 2021). Also, in support of this, previous studies on the effects of early psychosocial deprivation in humans found thicker cortex in institutionalized individuals only during adolescence and early adulthood, while at earlier ages, they found thinner cortex in the context of institutional rearing (Hodel et al., 2015; Sheridan et al., 2022). The more advanced thinning of PFC in the mother-reared group could thus be explained by both typical levels of synaptic pruning and progressive myelination in these cortical areas during adolescence, which is linked to better cognitive performance when it occurs during the expected sensitive period of development (Averbeck, 2022). However, the early closing of the expected sensitive window of PFC development could be linked to worse EF in the peer-reared group; i.e. early psychosocial deprivation accelerates the development of certain brain networks that leads to the premature closing of an adolescent plasticity window in PFC, which is related to greater cortical thickness in the long-term (Tooley et al., 2021).

Finally, accelerated or altered development of grey matter in PFC, reflected by less synaptic proliferation, early pruning, and/ or a slower myelination in the peer-reared group, could initially represent a compensatory mechanism after exposure to early psychosocial deprivation. Intriguingly, some research indicates that early social adversity can result in the prioritization of working memory development over inhibitory control (Ellis et al., 2017). In an unstable, threatening and/or deprived environment, it may be adaptive to prioritize the quick identification of salient stimuli and their location, and to not inhibit responses to these stimuli in order to act on them promptly; e.g. in the presence of a potentially threatening conspecific, or in the context of low food resources, it may be adaptive to identify related stimuli quickly and accurately and respond to them in a reactive manner especially in the absence of social support. Over time, however, this could end up being detrimental for various aspects of subsequent development. For instance, although this may be adaptive in macaque pre-puberty, this could then lead to less social success and more aggression and threats from other monkeys during adolescence, a time when peer relationships are becoming increasingly

important and the establishment of hierarchy takes place. There is also evidence that inhibitory control and information retention aspects of working memory are more heavily impacted by early psychosocial deprivation in children and adolescents compared to cognitive flexibility and monitoring aspects of working memory (Ellis et al., 2017; Johnson et al., 2021b; McDermott et al., 2013; Mittal et al., 2015). Our behavioural results provide some support for this difference in effects on certain aspects of working memory and inhibitory control. Only working memory maintenance (i.e.  $\lambda_1$ ) was impacted by early deprivation, while the more perceptual salience aspect of working memory (i.e.  $w_1$ ) was not different between rearing groups. In addition, inhibitory control (i.e.  $w_2$ ) was significantly worse for peer-reared compared to mother-reared animals in adulthood only. If the PFC of peer-reared animals already underwent extensive synaptic pruning and re-organization earlier on in development to adapt to their environment, they would likely be less flexible in adulthood. This could result in long-lasting impairment of inhibitory control and general EF, including randomness in decision making; i.e. this may reflect a sleeper effect. This idea is also supported by the results on cortical thickness, which show that dlPFC, an area implicated more in monitoring aspects of working memory, predicted this specific aspect of working memory in the same way in both groups, with thicker cortex predicting a worse outcome. In vlPFC, thickness predicted better working memory (both perceptual and long—term aspects) in mother-reared group, but more randomness in decision-making and impaired inhibitory control maintenance in peer-reared group. Therefore, compensatory mechanisms promoting particular aspects of working memory in the peer-reared group may also involve slightly different brain networks than those supporting these aspects in the mother-reared group; i.e. this represents an alternative developmental mechanism underlying working memory performance.

### ***White matter microstructure in fronto-parietal and fronto-striatal fiber tracts***

The results of the whole-brain white matter microstructure analysis using tract-based spatial statistics (TBBS) revealed an effect of early psychosocial deprivation on white-matter development in the superior longitudinal fasciculus (SLF), dorsal posterior (dpCR) and superior corona radiata (sCR), external capsule (EC), and corpus callosum (CC), but only when our three assessment time-points were combined. This somewhat aligns with previous research documenting effects of early psychosocial deprivation on fronto-parietal and fronto-striatal tracts in humans, as well as the corpus callosum (Sheridan et al., 2012, 2022). Higher radial

diffusivity (RD; see SI), likely signifying less myelination, in SLF, SCR, and EC in the mother-reared group could suggest an ongoing sensitive period of development, but lower RD reflecting accelerated development in the peer-reared group which led to the premature closure of a sensitive period (Larsen et al., 2022). Additionally, higher axial diffusivity (AD), perhaps signifying greater axonal organization and projection, in CC, dpCR and sCR, could suggest more advanced development in these areas in the mother-reared group, though understanding of typical development in terms of AD is currently limited compared to other DTI measures. Unfortunately, however, it is difficult to derive clear conclusions based on these findings due to the lack of change over time, with most other studies also having found differences in fractional anisotropy (FA) which was not the case here; FA can be driven by changes in RD and AD, and is commonly interpreted to reflect white matter integrity. A lack of differences in FA here could be related to sample size and a lack of power to detect significant differences using TBSS; this involves a large amount of multiple comparison corrections, and it is not possible to look at changes over time (i.e. separate analyses have to be run for each time-point).

The examination of white-matter integrity in specific regions of interest (ROIs) did reveal group and age effects on FA, partially supporting our hypotheses. Early psychosocial deprivation was related to differences in FA in two fronto-striatal tracts in the left hemisphere (ACR and ALIC). However, the peer-reared group had higher rather than lower FA compared to the mother-reared group in these tracts. This is in opposition to FA findings from previous studies concerning effects of institutionalization in childhood and adolescence (Johanna Bick & Nelson, 2015; Sheridan et al., 2022). This could be due to differences in age of assessment in these studies compared to the one presented here, and/or here it could again reflect a compensatory mechanism in the peer-reared group. This idea will be explored more later in the chapter, also considering links between effects on grey and white matter ROIs. Meanwhile, in the right ACR, the left SLF, and the left EC, we found higher FA in early adulthood compared to adolescence in both groups, which is in accordance with typical development in humans and macaques (Dean et al., 2015; Imperati et al., 2011; Pierre et al., 2008), and supported our hypothesis.

Specific white matter tracts were differentially associated with measures of EF, with these relationships also impacted differently by psychosocial deprivation. The integrity of the

SLF in both hemispheres was found to predict the general measure EF concurrently at both assessment time-points, in all animals. SLF integrity in adolescence also prospectively predicted inhibitory control (i.e.  $w_2$ ) in early adulthood in both groups. No other prospective relationships were found between white-matter integrity and EF. This lack of prospective findings could reflect a real lack of effects, but may also result from a lack of statistical power (this is also the case for the prospective cortical thickness analyses). However, differences in RD may have driven differences in FA (see SI) in SLF, with higher RD in this tract also being linked to worse general EF in both groups. This would be in line with the hypothesis that myelination is one of the mechanisms responsible for the closure of sensitive period (Larsen et al., 2022); as mentioned before in regards to the TBSS analysis, RD in SLF was higher in the mother-reared group. Rather than concurrently supporting EF, this could instead support future EF, in line with the typical protracted trajectory of EF refinement in later development. For the peer-reared group, accelerated development would be positively related to EF concurrently, but could lead to less flexible and impaired EF later on.

FA in fronto-striatal tracts was found to predict EF more widely in the mother-reared compared to the peer-reared group. In mother-reared animals, in early adulthood, higher concurrent integrity in the left ACR and right and left EC was related to better information retrieval/longer-term working memory maintenance (i.e.  $\lambda_1$ ), while higher integrity in the right ALIC was associated with worse perceptual salience (i.e.  $w_1$ ) and maintenance (i.e.  $\lambda_1$ ) aspects of working memory, as well as inhibitory control (i.e.  $w_2$ ). In addition, in adolescence, higher concurrent integrity in the left EC and in the right ALIC predicted worse working memory maintenance (i.e.  $\lambda_1$ ), but higher integrity in the right ALIC predicted better perceptual salience in working memory (i.e.  $w_1$ ). Interestingly, RD (see SI) seemed to drive FA changes in the ACR, with higher RD linked to better working memory in the mother-reared group. This may indicate that protracted development of these tracts is linked to better cognitive outcomes as part of normative development, reflecting a reorganization of these brain circuits during adolescence.

Some relationships between fronto-striatal integrity and EF were also found for the peer-reared group. In this group, higher integrity (FA) in the right ALIC was associated with better working memory in adolescence and early adulthood, with a stronger effect seen in adulthood. Higher integrity in the EC was related to worse working memory maintenance (i.e.



$\lambda_1$ ) in adolescence, but to better working memory in adulthood in peer-reared animals. Notably, the integrity of EC predicted working memory in the same direction in the mother-reared and peer-reared groups, but during adolescence, this relationship was stronger in the peer-reared group, and in early adulthood, this relationship was stronger in the mother-reared group. This suggests that early psychosocial deprivation can impact development of certain fronto-striatal tracts related to aspects of EF during adolescence, supporting recent findings that highlight the importance of the striatum and its connectivity in poor EF outcomes (Morris et al., 2016; Naze et al., 2022; Tian et al., 2020).

To summarise the results involving white-matter integrity in fronto-striatal and fronto-parietal tracts, a number of group and age effects were revealed in specific ROIs. Early deprivation was linked to differences in FA in fronto-striatal tracts, with the peer-reared group having higher white matter integrity compared to the mother-reared group. In early adulthood, FA in the right ACR, left SLF, and left EC was higher in both groups compared to adolescence. No effect of early deprivation was found on the SLF or EC. This contradicts earlier findings on the effects of early institutionalization on FA in these tract (Sheridan et al., 2022), however, this discrepancy may be associated with the ages at which assessment took place; here, SLF could have reached a higher level of maturity in both groups, with peer-reared animals 'catching-up' by early adulthood. However, general EF and future inhibitory control were related to SLF integrity, and longer-term working memory was related to EC integrity, highlighting the importance of looking at individual differences when looking at relations between brain and behaviour (there may not have been a group effect on SLF and EC, but individual differences in aspects of EF known to be worse in the peer-reared group were still associated with FA). The results showing higher FA in the ACR and ALIC in peer-reared animals may reflect accelerated development in this circuitry.

We did find fewer relationships between white matter integrity and EF in the peer-reared group compared to mother-reared group, and an opposite relationship between groups in ALIC. This may reflect impaired development in these tracts, greater variability in terms of development in the peer-reared group, and/or a lack of power to detect meaningful relationships. However, a potential explanation could also be that accelerated development in fronto-striatal circuits, as shown for cortical thickness in vLPFC, acts as a compensatory mechanism prioritizing monitoring aspects of working memory, with less inhibition also

helping animals to adapt to the early environment; but this leads to poor development of certain aspects of EF in the long-term. Interestingly, one study has shown FA decreases in fronto-parietal white matter following larger PFC lesions, but increases in some thalamo-cortical tracts during behavioral recovery (Adam et al., 2021). This implies that fronto-striatal tracts might rearrange along with fronto-parietal tracts to compensate for impairments in PFC, an idea that is supported by the findings presented in this chapter.

### ***Relationships between grey matter thickness and white matter integrity***

As noted above, the uncovering of significant age interactions for some brain measures but not others, with opposite directions sometimes found in adolescence and adulthood in the two rearing groups, may indicate that alterations in development of particular frontal networks serves as a compensatory mechanism in relation to PFC in the context of early psychosocial deprivation (Adam et al., 2021; Darki et al., 2020). Recent research has highlighted the involvement of fronto-striatal (or relatedly, fronto-thalamic) circuits in EF (Darki & Klingberg, 2015; Friedman & Robbins, 2022; Roy et al., 2022). The dlPFC is more closely connected to the SLF, and interestingly we found that thinner cortex in dlPFC and higher SLF white matter integrity was associated with better overall EF in both groups; note, white matter integrity in SLF during adolescence also predicted future inhibitory control in both groups. However, in the left SLF, we also found an effect of group on AD, with higher AD in mother-reared group compared to peer-reared group. In addition, higher RD was found in TBSS analyses in mother-reared group, and higher RD during adolescence and adulthood predicted worse EF in both groups. This fits with the idea of accelerated development in the fronto-parietal tract in the -reared group, with an overall increase in myelination of this tract, reflected by RD, suggesting earlier closure of an expected sensitive period in adolescence. This is also in line with the peer-reared group having thicker dlPFC, which predicted worse EF in both groups. Furthermore, the fact that higher white matter integrity in ALIC predicted better working memory in the peer-reared group could be related to the finding that thicker vlPFC predicted worse inhibitory control and decision-making in terms of randomness. In fact, ALIC connects the vlPFC with the striatum and thalamus (Haber et al., 2021; Petrides, 2005), and in line with discussion in the previous two sections of this chapter, we propose that higher integrity in the ALIC in the peer-reared animals reflects a compensatory mechanism prioritizing working memory over inhibitory control in early development. This mechanism

may impact the development of the vIPFC and related EF refinement. Another option could be that earlier impairment in PFC results in reorganization of fronto-striatal and fronto-parietal circuits. Further research is now needed clarify causal relationships in terms of how different neural networks interact and influence each other to predict different aspects of EF after psychosocial deprivation.

### ***Normative development of EF and its neural bases in macaques***

As well as important information on the effects of early psychosocial adversity, our findings also add to the literature about normative development of EF and its underlying neural correlates in macaques. Our results suggest a thinning in PFC across adolescence into adulthood in the dIPFC, with higher thickness in vIPFC compared to dIPFC perhaps reflecting later maturation. In addition, our results suggest a functional differentiation between dIPFC and vIPFC in all animals, and differential trajectories in their development in relation to EF. Thicker dIPFC predicted worse working memory in adulthood, while thicker vIPFC predicted better working memory, and differences in general EF and choice randomness (i.e. decision-making) across adolescence into adulthood. Overall, this is in line with previous research suggesting that cortical thinning in PFC occurs in macaques during adolescence (Brito & Noble, 2014; Ramirez et al., 2021), with earlier development and less changes in dIPFC seen across this period also related to working memory (Zhou et al., 2016). This is in keeping with the proposal of adolescence being a sensitive period for EF refinement and its neural correlates in macaques, as in humans, when major changes in PFC occur (Ferguson et al., 2021; Larsen et al., 2022; Sheridan et al., 2022; Thompson & Steinbeis, 2020; Verrico et al., 2011).

Additionally, white-matter integrity in fronto-striatal and fronto-parietal tracts predicted EF across time, revealing different developmental trajectories in various tracts as well. Interestingly, more typical developmental patterns in fronto-striatal tracts matched those in PFC; higher white matter integrity in SLF was associated with better overall performance, with integrity in SLF in adolescence also predicting future inhibitory control. In early adulthood, higher integrity in EC and ACR predicted better working memory and inhibitory control, and thicker dIPFC predicted worse working memory. This in line with evidence for cortical thinning and an increase of integrity in white matter tracts across development, as well as the relation between this and healthy cognitive outcomes. However, in early adulthood, higher integrity in ALIC predicted worse working memory, and thicker

vIPFC predicted better working memory and inhibitory control. This could be because vIPFC and related connectivity with other regions undergoes more protracted development, for example, and/or non-concurrent changes (i.e. one predicts the other prospectively). It is important to note that not all brain networks and regions development in parallel (Oldham & Fornito, 2019; Tau & Peterson, 2010). The results here are in keeping with this, and suggest a complex relationship between development in cortical regions, structural connectivity, and their interaction across development.

Finally, randomness in decision-making was only predicted by cortical thickness and not structural connectivity, which is in accordance with previous research in humans and macaques showing that PFC has a central role in decision-making (Oguchi et al., 2021).

### ***Strengths and limitations***

The current research has several strengths. Firstly, it is a longitudinal study focusing on a developmental transition that represents a critical time for refinement of EF, and one that may reveal delayed effects and/or long-term effects of early psychosocial adversity on neurocognitive development. Secondly, brain and behavioural measures were made at both time-points, which is a rarity in both human and macaque research on effects of ESA, and adds to our understanding of developmental trajectories after exposure to early adversity. Thirdly, as well as providing key insights into how early psychosocial deprivation impacts executive function and its underlying neural correlates in macaques, by including the mother-reared group, it also provides new information about typical versus atypical trajectories of development in macaques. Finally, the use of computational modelling to analyze behavior, utilization of advanced methods for the acquisition of very high-quality MRI data, and an integrative neuroscientific, ethological, psychological, and computational approach are also key strengths of this research.

Nevertheless, this research also possesses some limitations. Firstly, the sample size is limited, which may have influenced findings such as those for the TBSS and prospective analyses in particular. Furthermore, we have no EF measures prior to adolescence. The literature also demonstrates that other brain circuits, including limbic areas, also play an essential role in working memory and inhibitory control, therefore future studies should focus on wider and more complex brain networks in relation to EF development and early

psychosocial deprivation, in both human and macaques, to more fully comprehend how structural brain differences may contribute to differences in EF. For instance, future research could expand its focus beyond fronto-parietal and fronto-striatal tracts to include other limbic circuitry involved in executive function in emotional contexts. In general, replication of the findings presented in this chapter with larger samples and inclusion of more time-points across development will be important in future research.

It would also be useful to incorporate other measures of brain development such as changes in functional activity (e.g. fMRI, EEG) in order to understand how functional and structural changes interact to predict EF refinement in macaques. Another future direction of inquiry could be examination of the dopaminergic system, given its crucial role in both executive function and activity in fronto-striatal circuitry (Nour et al., 2019; Sajad et al., 2022). Finally, it will be interesting in future studies to see how a relationship between brain development and EF predict poor outcomes associated with EF, such as internalizing and externalizing symptoms, and symptoms of ADHD.

To conclude, this study aimed to examine the impact of early psychosocial deprivation in macaques on structural brain development associated with executive function in adolescence and early adulthood. Our results indicate that early deprivation has a negative influence on EF across this period via effects on vIPFC and connectivity in fronto-parietal and fronto-striatal networks. These findings also contribute significantly to our understanding of normative EF and neural bases in macaques, in addition to how these are impacted by early social adversity.

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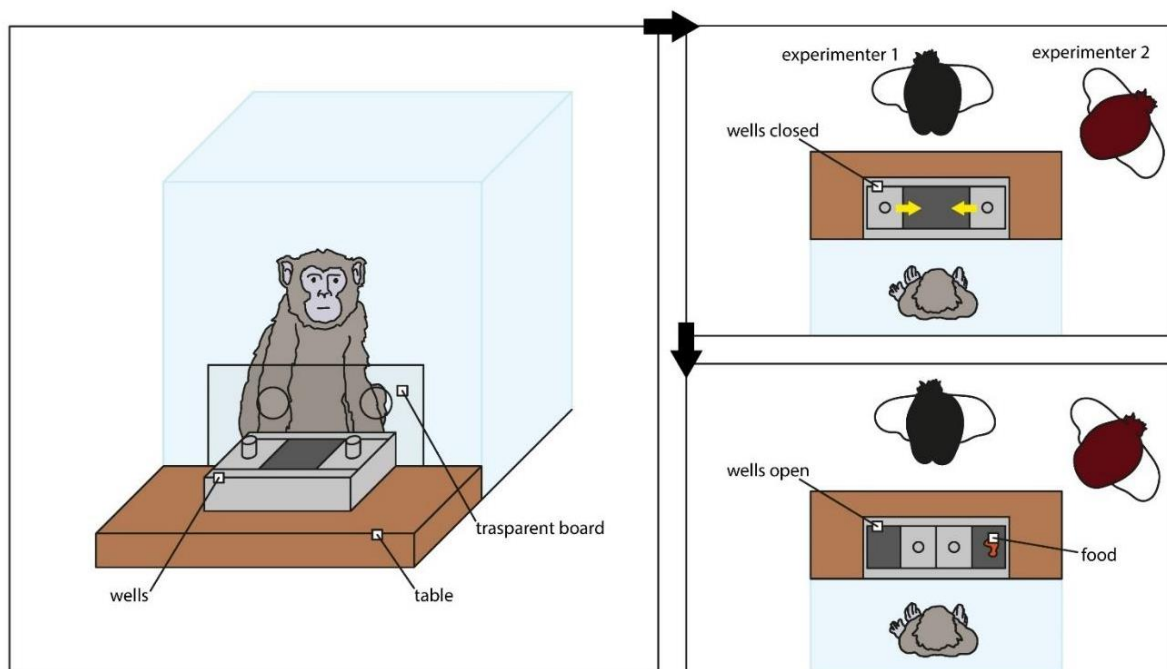
# Supplementary information

## Methods

### Subjects

All subjects were born and raised at the *Laboratory of Comparative Ethology at the National Institutes of Health, US*. Peer-reared animals were raised in a nursery with access to same-aged peers. See Shannon et al. (1998) for more information on the peer-rearing protocol. Rearing procedures were approved by the NICHD and the University of Maryland Animal Care and Use Committee, and adhered to the NIH Guide for the Care and Use of Laboratory Animals. Animals were relocated to their current location at the *Rousset Primatological Station, CNRS, France* at two years of age, and are housed altogether. As part of a wider longitudinal study, animals are temporarily relocated once a year to a nearby location in groups of 5-6 mixed mother- and peer-reared animals. All animals were kept alive at the end of the study.

### 'A-not-B' task set-up



**Figure S1.** *Task set-up.* A frontal view of the test enclosure is illustrated on the left. Two views from above are illustrated on the right: upper right, the wells are closed with the yellow arrows indicating a sliding mechanism; upper left, the wells are open and a piece of food is placed in one of them.



### **'A-not-B' task procedure**

For the first trial of each session, the delay period when visual and physical access to the wells was blocked lasted 2s, and then depending on the subject's performance, it was increased or decreased in subsequent trials. The delay period was decreased by 2s if two consecutive trials were incorrect, and was increased by 1s if two consecutive change trials were correct (Holmboe et al., 2008). Each subject completed two testing sessions at each assessment time point, with a maximum of 25 trials per session (i.e. 50 trials total per assessment time-point).

### **Video coding**

We coded a number of parameters offline from the video recordings made of each subject during the testing sessions. These included the actual length of the delay periods (i.e. from the moment the experimenter showed the food to the subject, to the moment the clear panel was removed to enable the subject to reach for the wells), inter-trial-interval (ITI) lengths, position of the subject in the testing enclosure during each trial, and other behaviours during and between trials that may have affected performance, such as locomotion, pacing, anxiety (i.e. self-scratch, self-groom, yawn), vocalizations, and threatening, fearful, or affiliative gestures. These behaviours were coded as being present or not during each trial and ITI. A random 15% of videos were coded by two researchers at each time-point to establish reliability for the original version of the task, and for the control version of the task at the second-time point (5 years). All reliability scores obtained between coders were very strong (i.e. all  $\kappa = 0.86-1.00$ ).

### **Computational model**

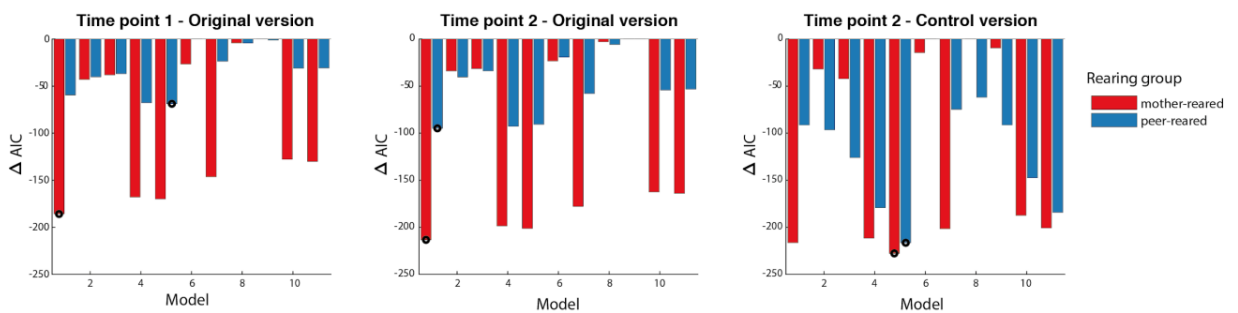
We tested 11 different computational models that differed in terms of the factors that contributed to the decision variable,  $z$ :

12) Working memory :  $z_t = w_1 S_t e^{-\lambda_1 d_t}$ , where  $w_1$  is the weight of this factor when the delay is 0,  $S_t$  is the side that food was hidden on in trial  $t$  (left = -1, right = 1), and  $d_t$  is the delay

13) Previous choice:  $z_t = w_2 R_{t-1} e^{-\lambda_2 (i_t + d_t)}$ , where  $w_2$  is the weight of this factor when the inter-trial interval and delay is 0,  $R_{t-1}$  is the response made on the previous trial (left = -1, right = 1), and  $i_t$  is the inter-trial interval before this trial.

- 14) Previous two choices:  $z_t = w_2(R_{t-1}e^{-\lambda_2(i_t+d_t)} + R_{t-2}e^{-\lambda_2(i_{t-1}+d_{t-1}+i_t+d_t)})$
- 15) Working memory and previous choice:  $z_t = w_1S_t e^{-\lambda_1 d_t} + w_2R_{t-1}e^{-\lambda_2(i_t+d_t)}$
- 16) Working memory and previous two choices:  $z_t = w_1S_t e^{-\lambda_1 d_t} + w_2(R_{t-1}e^{-\lambda_2(i_t+d_t)} + R_{t-2}e^{-\lambda_2(i_{t-1}+d_{t-1}+i_t+d_t)})$
- 17) Expected reward:  $z_t = w_3(v_{R,t} - v_{L,t})$ , where  $w_3$  is the weight of this factor,  $v_{R,t}$  is the expected reward at time  $t$  for choosing right, and  $v_{L,t}$  is the expected reward at time  $t$  for choosing left. Expected reward for each side was updated using the standard Rescorla-Wagner rule:  $v_{c,t+1} = v_{c,t} + \alpha(\hat{v}_{c,t} - v_{c,t})$ , where  $v_{c,t}$  is the expected reward for side  $c$  at time  $t$ ,  $\alpha$  is the learning rate, and  $\hat{v}_{c,t}$  is the actual reward received for choosing side  $c$  at time  $t$ .
- 18) Working memory and expected reward:  $z_t = w_1S_t e^{-\lambda_1 d_t} + w_3(v_{R,t} - v_{L,t})$
- 19) Previous choice and expected reward:  $z_t = w_2R_{t-1}e^{-\lambda_2(i_t+d_t)} + w_3(v_{R,t} - v_{L,t})$
- 20) Previous two choices and expected reward:  $z_t = w_2(R_{t-1}e^{-\lambda_2(i_t+d_t)} + R_{t-2}e^{-\lambda_2(i_{t-1}+d_{t-1}+i_t+d_t)}) + w_3(v_{R,t} - v_{L,t})$
- 21) Working memory, previous choice, and expected reward:  $z_t = w_1S_t e^{-\lambda_1 d_t} + w_2R_{t-1}e^{-\lambda_2(i_t+d_t)} + w_3(v_{R,t} - v_{L,t})$
- 22) Working memory, previous two choices, and expected reward:  $z_t = w_1S_t e^{-\lambda_1 d_t} + w_2(R_{t-1}e^{-\lambda_2(i_t+d_t)} + R_{t-2}e^{-\lambda_2(i_{t-1}+d_{t-1}+i_t+d_t)}) + w_3(v_{R,t} - v_{L,t})$

23)



**Figure S2. Model comparison.** Akaike information criterion (AIC) for each model relative to the worst model for both groups at each assessment time-point and task version. Filled circles represent the models with the lowest AIC.

Model comparison was performed using the Akaike information criterion (AIC; Akaike, 1973), a metric that captures the trade-off between model goodness of fit and complexity.

Lower AIC (relative to the worst model), indicates that the model better fits the data without being so complex that it overfits it. The sum of AIC for each subject was compared for each assessment time-point and task (Figure S2). Model 1 had the lowest AIC for the mother-reared group at time-points 1 and 2 and the peer-reared group at time point 2. Model 5 had the lowest AIC for the peer-reared group at time-point 1 and for both groups in the random version of the task. We therefore selected model 5 for the main analyses as it includes all the terms from model 1, and terms for the influence of the previous two choices.

### **Data analysis**

R v4.0.5 (R Core Team, 2020) and the lme4 v1.1-27.1 (Bates et al., 2015), lsmmeans v2.30.0 (Lenth, 2016), car v3.0.11 (Fox, Weisberg, 2019), and ggplot2 (Wickham, 2016) packages were utilized to conduct the analyses.

#### ***Data pre-processing***

Before analysis, we checked if any behaviours that occurred during the trial or the inter-trial interval (ITI) were affecting the model's ability to predict the subjects' responses. We found that locomotion during trials negatively impacted the model's prediction accuracy, so we excluded those trials from the analysis. We also removed trials with ITIs that were more than 2.5 standard deviations above the mean and excluded subjects with less than 25 remaining trials. We then checked for differences in ITI duration between the two rearing groups and we found no difference (see Massera et al, *in press*).

#### ***Trial exclusion***

Mean trials (out of the 50 trials for original task and 40 trials for the control task per subject) included for mother-reared animals were as follows: original task at the first time-point (3.5 years),  $M = 44.63$ ,  $SD = 6.36$ ; original task at the second time-point (5 years),  $M = 47.1$ ,  $SD = 2.96$ ; control task at the second time-point (5 years),  $M = 45.2$ ,  $SD = 5.69$ . Mean trials included for peer-reared animals were as follows: original task at the first time-point (3.5 years),  $M = 44.3$ ,  $SD = 5.61$ ; original task at the second time-point (5 years),  $M = 47.3$ ,  $SD = 4.49$ ; control task at the second time-point (5 years),  $M = 44.2$ ,  $SD = 6.17$ .

## Results

All descriptive statistics for the behavioural and MRI measures include in the analyses are presented in Table S1.

**Table S1. Descriptive statistics.** Behavioral measure of performance (i.e. cumulative score) in ‘A-not-B’ task at 3.5 and 5 years. Cumulative score M (SD) is the sum of all successful change trial delays and then divided by the number of total trials completed. Fitted parameters in ‘A-not-B’ task at 3.5 and 5 years M (SD):  $w_1$  (the weight of the working memory factor when the delay is 0),  $\lambda_1$  (decaying working memory trace of the food location),  $w_2$  (the weight of the choice factor when the inter-trial interval and delay is 0),  $\lambda_2$  (decaying trace of the previous choice), and  $\beta$  (choice stochasticity). Grey matter cortical ROIs M (SD) at 3.5 and 5 years: dlPFC – areas 46d, 46v, 9/46d, 9/46v; vlPFC – areas 44, 45A, 45B. White matter ROIs M (SD) at 3.5 and 5 years: superior longitudinal fasciculus (SLF), anterior corona radiata (ACR), anterior limb of internal capsule (ALIC), external capsule (EC).

	Group	
	Mother-reared	Peer-reared
<b><u>Cumulative score</u></b>		
3.5 years	0.643 (0.316)	0.265 (0.204)
5 years	0.712 (0.4)	0.279 (0.244)
<b><u>Fitted parameters</u></b>		
<b><u><math>w_1</math></u></b>		
3.5 years	0.494 (0.387)	0.286 (0.255)
5 years	0.363 (0.339)	0.177 (0.134)
<b><u><math>\lambda_1</math></u></b>		
3.5 years	0.09 (0.301)	0.3 (0.483)
5 years	0.1 (0.316)	0.5 (0.527)
<b><u><math>w_2</math></u></b>		
3.5 years	0.51 (0.486)	- 0.025 (0.657)
5 years	0.07 (0.686)	0.495 (0.438)
<b><u><math>\lambda_2</math></u></b>		
3.5 years	0.203 (0.182)	0.182 (0.254)
5 years	0.134 (0.139)	0.194 (0.199)
<b><u><math>\beta</math></u></b>		
3.5 years	9.029 (1.568)	6.577 (3.196)
5 years	7.664 (2.606)	8.157 (2.669)

<b><u>Grey matter ROIs</u></b>	<b>Mother-reared</b>	<b>Peer-reared</b>
<b><u>dIPFC</u></b>	<b>cortical thickness (mm)</b>	
<b><u>right 46d</u></b>		
3.5 years	3.49 (0.28)	3.627 (0.213)
5 years	3.505 (0.55)	3.681 (0.246)
<b><u>left 46d</u></b>		
3.5 years	3.412 (0.205)	3.725 (0.324)
5 years	3.435 (0.507)	3.762 (0.198)
<b><u>right 46v</u></b>		
3.5 years	3.434 (0.218)	3.638 (0.198)
5 years	3.232 (0.35)	3.548 (0.18)
<b><u>left 46v</u></b>		
3.5 years	3.528 (0.155)	3.668 (0.201)
5 years	3.414 (0.268)	3.59 (0.242)
<b><u>right 9/46d</u></b>		
3.5 years	3.624 (0.244)	3.77 (0.224)
5 years	3.418 (0.751)	3.745 (0.194)
<b><u>left 9/46d</u></b>		
3.5 years	3.665 (0.21)	3.76 (0.31)
5 years	3.508 (0.792)	3.85 (0.251)
<b><u>right 9/46v</u></b>		
3.5 years	3.58 (0.24)	3.935 (0.154)
5 years	3.387 (0.731)	3.892 (0.18)
<b><u>left 9/46v</u></b>		
3.5 years	3.58 (0.232)	3.908 (0.273)
5 years	3.453 (0.618)	3.837 (0.295)
<b><u>vIPFC</u></b>	<b>cortical thickness (mm)</b>	
<b><u>right 44</u></b>		
3.5 years	4.013 (0.186)	4.083 (0.197)

5 years	3.745 (0.961)			4.071 (0.228)		
<i>left 44</i>						
3.5 years	3.908 (0.145)			4.08 (0.134)		
5 years	3.584 (0.902)			4.08 (0.138)		
<i>right 45A</i>						
3.5 years	4.63 (0.147)			4.744 (0.097)		
5 years	4.244 (1.177)			4.755 (0.094)		
<i>left 45A</i>						
3.5 years	4.588 (0.19)			4.68 (0.145)		
5 years	4.251 (1.006)			4.677 (0.157)		
<i>right 45B</i>						
3.5 years	4.2 (0.177)			4.429 (0.132)		
5 years	3.879 (1.042)			4.39 (0.122)		
<i>left 45B</i>						
3.5 years	4.056 (0.179)			4.371 (0.11)		
5 years	3.769 (0.968)			4.363 (0.109)		
	<b>Mother-reared</b>			<b>Peer-reared</b>		
<b><i>White matter ROIs</i></b>	<b>FA</b>	<b>RD</b>	<b>AD</b>	<b>FA</b>	<b>RD</b>	<b>AD</b>
<i>right SLF</i>						
3.5 years	0.514 (0.028)	0.839 (0.054)	1.208 (0.043)	0.503 (0.023)	0.831 (0.104)	1.156 (0.051)
5 years	0.527 (0.017)	0.785 (0.06)	1.193 (0.062)	0.504 (0.018)	0.81 (0.095)	1.168 (0.04)
<i>left SLF</i>						
3.5 years	0.512 (0.033)	0.688 (0.03)	1.2 (0.054)	0.5 (0.018)	0.653 (0.064)	1.15 (0.043)
5 years	0.533 (0.022)	0.67 (0.084)	1.193 (0.057)	0.5 (0.02)	0.621 (0.021)	1.14 (0.02)
<i>right ACR</i>						
3.5 years	0.513 (0.021)	0.681 (0.022)	1.192 (0.055)	0.519 (0.033)	0.67 (0.046)	1.182 (0.052)
5 years	0.527 (0.02)	0.668 (0.027)	1.17 (0.033)	0.536 (0.018)	0.653 (0.024)	1.193 (0.05)
<i>left ACR</i>						

3.5 years	0.513 (0.02)	0.714 (0.03)	1.209 (0.078)	0.536 (0.027)	0.709 (0.024)	1.216 (0.052)
5 years	0.529 (0.025)	0.695 (0.024)	1.186 (0.036)	0.54 (0.02)	0.72 (0.044)	1.208 (0.03)
<i>right ALIC</i>						
3.5 years	0.617 (0.028)	0.705 (0.032)	1.419 (0.089)	0.627 (0.037)	0.695 (0.044)	1.443 (0.139)
5 years	0.63 (0.035)	0.712 (0.052)	1.433 (0.13)	0.619 (0.035)	0.658 (0.041)	1.341 (0.09)
<i>left ALIC</i>						
3.5 years	0.606 (0.027)	0.713 (0.041)	1.396 (0.074)	0.64 (0.04)	0.709 (0.032)	1.466 (0.159)
5 years	0.623 (0.028)	0.709 (0.04)	1.417 (0.1)	0.631 (0.025)	0.694 (0.04)	1.364 (0.068)
<i>right EC</i>						
3.5 years	0.468 (0.031)	0.762 (0.033)	1.212 (0.051)	0.473 (0.022)	0.746 (0.051)	1.204 (0.066)
5 years	0.483 (0.025)	0.758 (0.067)	1.231 (0.057)	0.484 (0.021)	0.729 (0.035)	1.209 (0.028)
<i>left EC</i>						
3.5 years	0.461 (0.022)	0.739 (0.033)	1.222 (0.039)	0.475 (0.02)	0.717 (0.042)	1.216 (0.078)
5 years	0.478 (0.033)	0.739 (0.051)	1.227 (0.044)	0.479 (0.03)	0.706 (0.035)	1.202 (0.032)

**Differences between groups in specific white matter tracts associated with EF and early adversity (AD and RD)**

All the model results are shown in Table S2.

A significant main effect of group was also found in the left SLF in AD [ $\chi^2(1) = 5.153, p = 0.023$ ], with the mother-reared group having higher AD compared to peer-reared group. No other significant effects were observed in RD and AD in the left SLF.

Additionally, we identified a significant interaction between group and time point on AD in the left ALIC [ $\chi^2(1) = 4.203, p = 0.04$ ], however follow-up analyses were not significant. There was no effect of group, time point or group by time point interaction in the left hemisphere for RD. No significant results in the right ALIC for RD and AD.

No effects were found for RD or AD in right and left ACR. No significant effects were observed for RD and AD in the right and left EC.

**Table S2: Significant results summary.** Main effects of group and time point and their interaction in all models with ROIs.

<b>ROIs - Group and time point effects</b>			
<b>Cortical Thickness (CT)</b>	<b>Main effects and interactions</b>	<b><math>\chi^2(1)</math></b>	<b><i>p</i> value</b>
<b><i>dIPFC</i></b>			
Left - 46d	Group	7.642	0.006
Right - 46v	Group	3.960	0.047
	Year	8.301	0.004
Right - 9/46d	Group	4.263	0.039
Right - 9/46v	Group	4.884	0.027
Left - 9/46v	Group	5.54	0.019
<b><i>vIPFC</i></b>			
Right - 45B	Group	10.847	< 0.001
Left - 45B	Group	22.1	< 0.001
<b>Tract and diffusivity (DTI) measures</b>	<b>Main effects and interactions</b>	<b><math>\chi^2(1)</math></b>	<b><i>p</i> value</b>
Left - SLF FA	Year	5.712	0.0168
Left - SLF AD	Group	5.154	0.023
Right - ACR FA	Year	4.647	0.031
Left - ACR FA	Group	4.632	0.031
	Year	3.638	0.056
Left - ALIC FA	Group	8.199	0.004
Left - ALIC AD	Group:Year	4.203	0.04



Left - EC FA	Year	4.97	0.026
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### **Concurrent DTI ROI-EF relationships (AD and RD)**

All the model results are shown in Table S3.

For SLF, higher RD was also found to be related to lower performance (cumulative score) in the right hemisphere [ $\chi^2(1) = 8.519, p = 0.003$ ]. No significant relationships between AD and cumulative core were found. We did not find any other significant effects of time point, group, or interactions for SLF for other outcome variables.

For ACR, in the analyses predicting  $\lambda_1$ , significant interactions were also found between RD, group, and time-point in the left hemisphere [ $\chi^2(1) = 1.9568e+10, p < 0.001$ ]. At 3.5 years, for the mother-reared group, higher RD was related to higher  $\lambda_1$  (i.e. faster working memory decay/worse working memory) [ $z(1) = 56181.33, p < 0.001$ ], while for the peer-reared group, higher RD was related to lower  $\lambda_1$  (i.e. slower working memory decay/better working memory) [ $z(1) = -166468.38, p < 0.001$ ]. At 5 years, the opposite was true, with the mother-reared group having higher RD related to lower  $\lambda_1$  (i.e. slower working memory decay/better working memory) [ $z(1) = -91022.77, p < 0.001$ ], and the peer-reared group having higher RD related to higher  $\lambda_1$  (i.e. faster working memory decay/worse working memory) [ $z(1) = -91022.770, p < 0.001$ ]. Therefore, the relationship between RD and  $\lambda_1$  was significantly different between the two rearing groups at 3.5 years [ $z(1) = 114274.02, p < 0.001$ ], and at 5 years [ $z(1) = -21006.15, p < 0.001$ ]. The relationship between RD and  $\lambda_1$  was also significantly different in the mother-reared group [ $z(1) = 44924.73, p < 0.001$ ], and in the peer-reared group [ $z(1) = -69245.63, p < 0.001$ ] between 3.5 years and 5 years. In the analyses predicting  $\lambda_1$ , a significant interaction was also revealed between AD, group, and time-point in the left hemisphere [ $\chi^2(1) = 2.1800e+08, p < 0.001$ ]. At 3.5 years, for both groups, higher AD was related to lower  $\lambda_1$  (i.e. slower working memory decay/better working memory), [mother-reared,  $z(1) = -48474.28, p < 0.001$ ; peer-reared,  $z(1) = -68847.19, p < 0.001$ ] but with the peer-reared group having a stronger negative relationship compared to the mother-reared group [ $z(1) = 40446.83, p < 0.001$ ]. At 5 years, the opposite was true: for both groups, higher AD was related to higher  $\lambda_1$  (i.e. faster working memory decay/worse working memory) [mother-reared,  $z(1) = 31139.79, p < 0.001$ ; peer-reared,  $z(1) = 26321.17, p < 0.001$ ], but with the peer-reared group having

again a stronger negative relationship [ $z(1) = -2061.84, p < 0.001$ ]. The relationship between AD and  $\lambda_1$  was also significantly different between 3.5 years and 5 years in the mother-reared group [ $z(1) = -94945.48, p < 0.001$ ], and in the peer-reared group [ $z(1) = -113943.17, p < 0.001$ ]. No other significant relationships were found in analyses predicting the other model parameters.

For ALIC, for the analysis of  $w_1$ , we found a significant interaction between AD, group, and time point in the right hemisphere [ $\chi^2(1) = 6.492, p = 0.011$ ]. For the mother-reared group at 5 years, higher AD was related to lower  $w_1$  (i.e. worse working memory) compared to 3.5 years [ $t(1) = 2.266, p = 0.034$ ] [ $t(1) = -2.207, p = 0.035$ ]. No significant results were found for radial diffusivity (RD). Additionally, for the analysis of  $\lambda_1$ , in the right hemisphere, we found a significant interaction between AD, group, and time point [ $\chi^2(1) = 4.0404e+09, p < 0.001$ ]. At both time-points for the mother-reared group, higher AD was related to higher  $\lambda_1$  (i.e. faster working memory decay /worse working memory) [3.5 years,  $z(1) = 7367.1, p < 0.001$ ; 5 years,  $z(1) = 15898.12, p < 0.001$ ], with a stronger relationship at 5 years [ $z(1) = -12743.04, p < 0.001$ ]. On the contrary, for the peer-reared group, higher AD was related to lower  $\lambda_1$  (i.e. slower working memory decay /better working memory) [3.5 years,  $z(1) = -22653.57, p < 0.001$ ; 5 years,  $z(1) = -48411.86, p < 0.001$ ], with a stronger relationship at 5 years [ $z(1) = 38208.17, p < 0.001$ ]. The relationship between AD and  $\lambda_1$  also differed between the two rearing groups at 3.5 years [ $z(1) = 40680.97, p < 0.001$ ], and at 5 years [ $z(1) = 72303.46, p < 0.001$ ]. No relationship with RD was found. Finally, for the analysis of  $w_2$ , a significant interaction between AD, group, and time point in the right hemisphere was found [ $\chi^2(1) = 6.926, p = 0.008$ ]. At 3.5 years, for the peer-reared group, higher AD was related to higher  $w_2$  (i.e. repeating previous choices more frequently/worse response inhibition) [ $t(1) = 2.05, p = 0.049$ ], differing from the mother-reared group at the same time point [ $t(1) = -2.118, p = 0.042$ ]. No relationship with RD was found.

For EC, no significant relationships were found between RD and AD, and  $\lambda_1$ .

**Table S3: Significant results summary.** Main effects and interaction effects in all models with ROIs and EF.

<b>ROIs - behaviour models</b>				
<b>Cortical Thickness (CT) measures</b>	<b>Behavioural measures</b>	<b>Main effects and interactions</b>	<b><math>\chi^2(1)</math></b>	<b><i>p</i> value</b>
<b><i>dIPFC</i></b>				
Left - 9/46d	$w_1$	Year	10.317	0.001
		CT:Year	10.909	< 0.001
Right - 9/46v	$w_1$	CT	11.001	< 0.001
		Year	10.445	0.001
		CT:Year	11.285	< 0.001
Right - 46d	$\beta$	CT:Group	8.657	0.003
<b><i>vIPFC</i></b>				
Right - 44	Score	Year	8.676	0.003
		CT:Year	8.61	0.003
Right - 45B	Score	Year	18.751	< 0.001
		CT:Year	18.735	< 0.001
Left - 45B	$w_1$	CT	11.015	< 0.001
		Group	9.289	0.002
		CT:Group	9.978	0.002
		CT:Year	9.031	0.003
Right - 45A	$\lambda_1$	Group	83.551	< 0.001
		Year	98.576	< 0.001
		CT:Year	8.901	0.003
		Group:Year	89.615	< 0.001
		CT:Group:Year	9.251	0.002
Right - 45B	$\lambda_2$	Group	25.824	< 0.001
		CT:Group	25.661	< 0.001

		Group:Year	8.592	0.003
		CT:Group:Year	8.517	0.003
Left - 45A	$\beta$	Group:Year	8.705	0.003
		CT:Group:Year	9.117	0.002
Right - 45B	$\beta$	CT:Group	8.596	0.003
<b>Tract and diffusivity (DTI) measures</b>	<b>Behavioural measures</b>	<b>Main effects and interactions</b>	<b><math>\chi^2(1)</math></b>	<b><i>p</i> value</b>
Right - SLF FA	Score	DTI	10.137	0.001
		Year	7.589	0.006
		DTI:Year	7.54	0.006
Left - SLF FA	Score	DTI	16.106	< 0.001
Right - SLF RD	Score	DTI	8.519	0.003
		Group	8.572	0.003
Left - ACR FA	$\lambda_1$	Year	7229.847	< 0.001
		DTI:Year	1.742.978	< 0.001
		Group:Year	684.089	< 0.001
		DTI:Group:Year	2.043.796	< 0.001
Left - ACR RD	$\lambda_1$	DTI	9.9258e+08	< 0.001
		Group	6.8112e+09	< 0.001
		Year	1.0249e+09	< 0.001
		DTI:Group	1.3059e+10	< 0.001
		DTI:Year	2.0182e+09	< 0.001
		Group:Year	9.6751e+09	< 0.001
		DTI:Group:Year	1.9568e+10	< 0.001
Left - ACR AD	$\lambda_1$	DTI	2.3696e+09	< 0.001
		Group	1.1163e+09	< 0.001
		Year	1.4404e+10	< 0.001
		DTI:Group	6.1820e+08	< 0.001
		DTI:Year	1.0331e+10	< 0.001

		Group:Year	3.1055e+08	< 0.001
		DTI:Group:Year	2.1800e+08	< 0.001
Right - ALIC FA	$w_1$	DTI	7.864	0.005
		Year	12.94	< 0.001
		DTI:Group	7.966	0.005
		DTI:Year	13.385	< 0.001
		Group:Year	15.122	< 0.001
		DTI:Group:Year	15.234	< 0.001
		Right - ALIC AD	$w_1$	Year
DTI:Year	5.587			0.018
Group:Year	6.572			0.01
DTI:Group:Year	6.492			0.01
Right - ALIC FA	$\lambda_1$	DTI	9.7835e+07	< 0.001
		Group	7.9330e+07	< 0.001
		Year	1.6785e+07	< 0.001
		Sex	2.7203e+03	< 0.001
		DTI:Group	1.9397e+08	< 0.001
		DTI:Year	4.2036e+07	< 0.001
		Group:Year	1.0101e+07	< 0.001
		DTI:Group:Year	2.6082e+07	< 0.001
Right - ALIC AD	$\lambda_1$	DTI	4.1621e+07	< 0.001
		Group	2.2523e+09	< 0.001
		Year	1.0689e+09	< 0.001
		DTI:Group	1.1024e+09	< 0.001
		DTI:Year	4.1351e+08	< 0.001
		Group:Year	7.7152e+09	< 0.001
		DTI:Group:Year	4.0404e+09	< 0.001
Right - ALIC FA	$w_2$	Group:Year	8.98	0.003
		DTI:Group:Year	8.134	0.004

Right - ALIC AD	$w_2$	Group	5.549	0.018
		Year	4.694	0.03
		DTI:Group	4.894	0.027
		DTI:Year	4.319	0.038
		Group:Year	7.929	0.005
		DTI:Group:Year	6.926	0.008
Right - EC FA	$\lambda_1$	Year	113.265	< 0.001
		DTI:Year	168.215	< 0.001
		Group:Year	106.901	< 0.001
		DTI:Group:Year	120.539	< 0.001
Left - EC FA	$\lambda_1$	DTI	7.4265e+03	< 0.001
		Group	9.1017e+06	< 0.001
		Year	8.9928e+09	< 0.001
		DTI:Group	6.1987e+07	< 0.001
		DTI:Year	4.3075e+10	< 0.001
		Group:Year	5.0013e+09	< 0.001
		DTI:Group:Year	2.5229e+10	< 0.001

### **Prospective DTI-EF relationships**

No significant relationships were found between RD and AD, and  $w_2$ .

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## **CHAPTER 5.**

### **General discussion**



## Summary of results

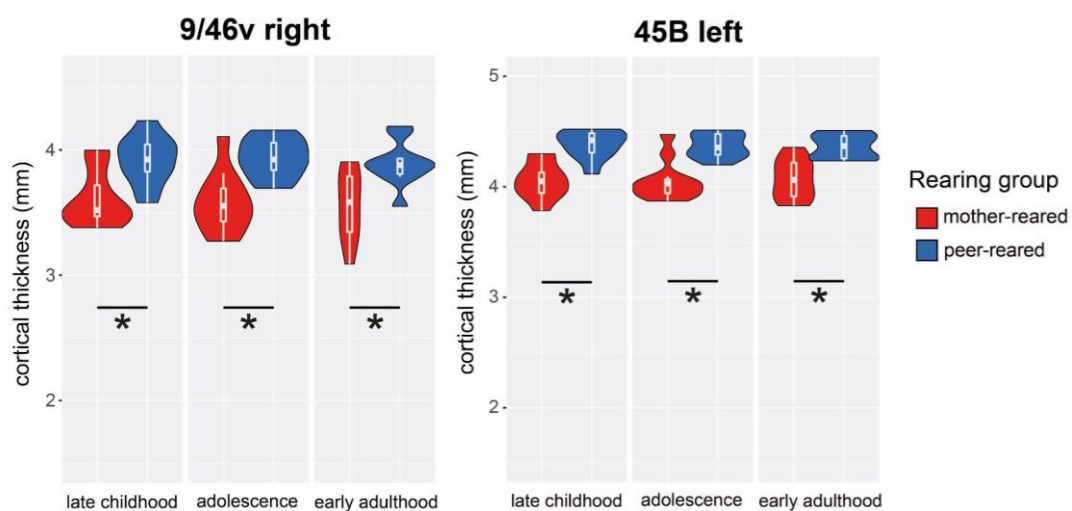
The main purpose of this thesis was to investigate the longitudinal effects of early psychosocial deprivation on macaque executive function (EF), as well as the neural mechanisms through which such adverse early experience may lead to deficits in EF. Findings demonstrate that early deprivation can result in long-lasting EF impairments, with structural alterations in the prefrontal cortex (PFC) and both cortico-cortical and cortico-subcortical connectivity of PFC modulating the relationship between early rearing conditions and different measures of EF. This is the first set of studies to investigate explicitly how early psychosocial adversity impacts EF in macaques, and is one of the first to look at EF and associated brain development longitudinally in adolescence and adulthood after exposure to early adversity. Altogether, these findings provide important insights into the neurocognitive mechanisms that may underlie poor long-term developmental trajectories linked to cognitive aspects of self-regulation in those exposed to early psychosocial deprivation, and further our understanding of the factors that may increase risk for poor outcomes such as psychopathology and ADHD-like symptoms in this population.

## More detailed results

Results from Chapter 3 supported the hypothesis that peer-rearing would be related to worse EF across adolescence into adulthood, in keeping with human research on the effects of early institutionalization on EF (Wade et al., 2019, 2022a). This was found in terms of general EF, and via the novel computational modeling approach used to functionally decompose EF mechanisms contributing to 'A not B' task performance, in terms of working memory across time and inhibitory control in adulthood.

Concerning structural brain development, differences presented in Chapter 4 in ventrolateral and dorsolateral PFC (i.e. cortical thickness) and in white matter tracts (i.e. fractional anisotropy) connecting the PFC with the parietal cortex and striatum were found between the mother-reared and peer-reared groups. As predicted, cortical thickness in these PFC regions was greater in the peer-reared group. This is in keeping with human studies of early institutional rearing effects on structural changes in PFC (Mackes et al., 2020; M. A. Sheridan et al., 2022).

Additionally, results are presented in Appendix B of this thesis from analyses of structural brain development including all three assessment time-points from the wider project (late childhood, adolescence, and early adulthood), rather than just the two time-points included in analyses in Chapter 4 (adolescence and early adulthood); i.e. the two ages at which EF was assessed; showed that in more dorsal dIPFC regions (i.e. right 46v), cortical thickness decreased across time in both rearing groups. Conversely, in more ventral regions of dIPFC (right 9/46v) and in the majority of vIPFC regions (left 44, right and left 45b), peer-reared animals had higher cortical thickness than mother-reared animals across time (Figure 1).



**Figure 1.** Group differences in cortical thickness in right 9/46v areas (dIPFC) and left 45B area (vIPFC). Across all time-points, greater cortical thickness was found in the peer-reared (blue) versus mother-reared (red) group in the right 9/46v and in the left 45B areas. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting  $\pm$  SE and \* denoting significant differences. Details on the analysis can be found in Appendix B.

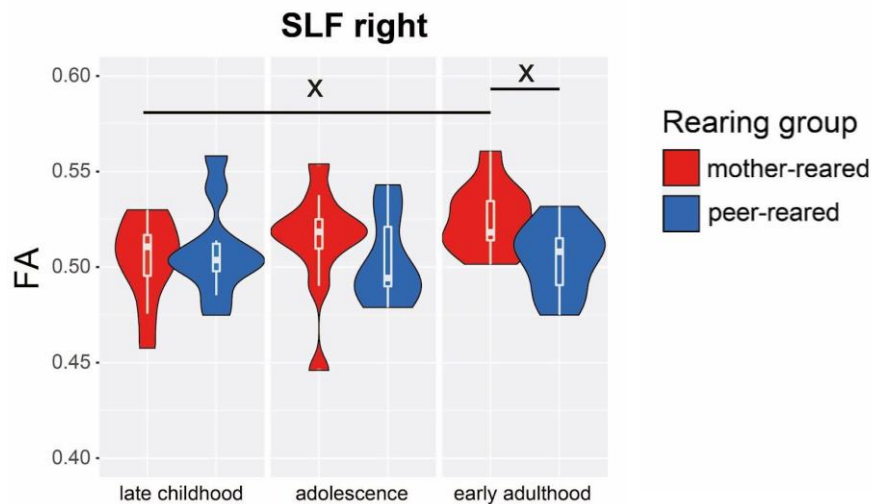
The lack of group effects for more dorsal regions of dIPFC could imply that such regions develop similarly in both groups, or that any differences would have been more likely at earlier stages of development with peer-reared groups having thinner cortex initially and mother-reared catching up by late childhood. This, along with the group difference found in more ventral regions of dIPFC across time, is in line with previous studies on the effects of early psychosocial deprivation in humans which found thinner cortex across childhood, but thicker cortex during adolescence and early adulthood in the context of institutional rearing (Hodel et al., 2015; M. A. Sheridan et al., 2022). However, research including more assessment time-points covering a longer developmental time-period in humans and macaques is now

necessary, as well as inclusion of larger sample sizes and the use of different statistical approaches, to make firmer conclusions about developmental trajectories of PFC thickness that may differ after psychosocial deprivation.

Some interesting but unexpected findings were revealed in terms of structural brain connectivity, with greater white-matter integrity (i.e. higher fractional anisotropy) found in some fronto-striatal tracts in peer-reared animals. This was in contrast to the predicted lower white matter integrity compared to mother-reared animals, which would have been in accordance with previous literature (Johanna Bick & Nelson, 2015; M. A. Sheridan et al., 2022).

Notably, cortical thickness in vIPFC and white matter integrity in the anterior limb of the internal capsule (ALIC) predicted EF differences in the peer-reared group; thicker vIPFC predicted worse inhibitory control in peer-reared animals, but greater ALIC integrity predicted better working memory in this group. Small lesions in PFC have been linked to an increase in fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF), as well as in thalamocortical tracts which include connectivity between striatum and PFC. However, *larger* lesions in the PFC lead to decreases in FA in the SLF, but still an increase in thalamocortical tracts. This indicates that more extensive damage can activate somewhat different pathways of compensation to support behavioural recovery via thalamocortical connectivity (Adam et al., 2021).

We did not find clear differences in SLF between the groups in Chapter 4, however, the additional analysis reported in Appendix B including all three-time points suggests an increase in the integrity of this tract across adolescence into early adulthood, in the mother-reared group only (Figure 2). This, as well as the results concerning vIPFC and increased ALIC (i.e. fronto-striatal) FA in the peer-reared group, are in keeping with the latter compensatory mechanism, whereby profound deficits in PFC lead to decreased integrity in fronto-parietal tracts (SLF), but to increased integrity in fronto-striatal tracts (ALIC). This could support EF in the peer-reared group. However, it is possible that this mechanism promotes only certain components of EF, such as working memory in earlier development, which may be at the expense of inhibitory control.



**Figure 2.** Group differences in FA in the right superior longitudinal fasciculus (SLF). In the right SLF, a trend was found suggesting that integrity of SLF was greater in the mother-reared (red) versus peer-reared (blue) group in early adulthood, with integrity in the mother-reared group differing from late childhood to early adulthood. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting  $\pm$  SE and X denoting trends ( $p < 0.055$ ). Details on the analysis can be found in Appendix B.

Other research has found that in the context of early psychosocial deprivation, inhibitory control and information retrieval are impacted negatively, while cognitive flexibility, monitoring, and certain aspects of working memory are not, or are even enhanced (Ellis et al., 2017; Nweze et al., 2021; Sheehy-Skeffington, 2020; Young et al., 2018). Increased fronto-striatal integrity such as that found here may reflect this prioritization of working memory. More flexible behaviour linked to working memory and less inhibitory control could represent an adaptive mechanism linked to changes in brain development that is initially beneficial in the context of early psychosocial deprivation, but could result in the premature closing of typical neural plasticity windows, and therefore lead to poor EF outcomes in adolescence and adulthood. Network analyses could help to test this idea more explicitly in the future to see how changes in different PFC networks may interact together to promote certain components of EF versus others after early psychosocial deprivation.

## **What does this suggest about neurocognitive mechanisms underlying poor outcomes after early psychosocial deprivation?**

The findings in this thesis provide support for early psychosocial deprivation in macaques having a significant impact on neural plasticity, which is likely related to poor executive function in adolescence and adulthood. While proliferation and pruning of synaptic connections in the PFC occurs in infancy, pruning of these connections also occurs extensively in adolescence (Huttenlocher, 1999; Shaw et al., 2008; Spear, 2013). In the context of psychosocial deprivation, the lack of socio-cognitive stimulation in the early caregiving environment may decrease synaptic proliferation or early pruning in regions of PFC and parietal cortex. This, in turn, may lead to the premature closing of neural plasticity windows, therefore rendering these regions less malleable during subsequent sensitive periods of development when experience plays a vital role in healthy neural development (e.g. adolescence). This may explain why in previous research, reduced gray matter volume and cortical thinning in those exposed to early institutional rearing has been found earlier in childhood (Hodel et al., 2015; McLaughlin et al., 2014), but increased thickness in adolescence (Sheridan et al., 2022). The results presented in Chapter 4, showing thicker cortex in vIPFC and higher integrity in fronto-striatal tracts across time in the peer-reared group could reflect this lack of flexibility. In addition, results in the Appendix B also suggest that peer-reared animals have lower integrity in fronto-parietal connectivity in early adulthood. This is also in line with the idea of accelerated development in these regions, and thus less malleability later on.

Although plasticity models have focused mostly on effects on cortical development, effects of reduced plasticity and differences in cortico-subcortical connectivity has also been hypothesized. This is supported by previous findings of altered structural connectivity in salience networks in macaques and in humans (Howell et al., 2019; Sheridan et al., 2022), and the findings presented in Chapter 4. Interestingly, fewer changes were found in terms of connectivity in the peer-reared group over time compared to the mother-reared group overall. This, along with the cortical thickness results, again supports the idea that early psychosocial deprivation, via altered plasticity mechanisms, may lead to a premature closing of neural plasticity windows, and thus less changes and refinement in adolescence.

Although the main results presented in Chapters 3, 4, and Appendix B do suggest that early deprivation affects neural plasticity mechanisms and the premature closing of sensitive periods, this does not mean that other mechanisms do not affect brain development linked to EF. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has also been linked to early psychosocial deprivation (Callaghan et al., 2019; Silvers et al., 2017; Tottenham et al., 2011). Indeed, evidence suggests that early life stress linked to social adversity negatively affects GABAergic and glutamate release in the PFC and other subcortical areas (e.g. amygdala), and that this is related to a reduction in inhibitory regulation but an increase in excitatory regulation (Acosta & Acosta, 2017; Chen et al., 2022; Hanson & Nacewicz, 2021; Suwaluk & Chutabhakdikul, 2022). This affects the excitatory/inhibitory balance in these brain regions, with protracted reduction in GABA then preventing the opening of sensitive developmental periods. A key role of GABAergic increase and decrease in the excitatory/inhibitory ratio may be the opening of a sensitive period in the association cortex in addition to the sensory cortices (Caballero et al., 2021; Larsen et al., 2022). Dysregulation of this mechanism has been associated with a number of psychopathologies involving EF impairment (Ghosal et al., 2017; Hanson & Nacewicz, 2021; Suwaluk & Chutabhakdikul, 2022). Therefore, both changes in neural plasticity and HPA-axis dysregulation could contribute to the poor EF observed here in the peer-reared group during adolescence and into adulthood.

## **How do findings fit with conceptual models of how early psychosocial deprivation versus other forms of adversity relate to poor outcomes?**

A number of conceptual models have been proposed to explain how the different neural mechanisms discussed in the previous section may contribute to poor outcomes in the context of different aspects of early social adversity. For example, specificity models (e.g. Wyman, 2003) consider the independent effects of particular adverse experiences on different developmental outcomes via distinguishable anatomical and functional neural pathways. Cumulative risk models define adversity as the combination of multiple risk factors, which are combined into both overlapping and divergent risk factors into one composite score (e.g. Evans et al., 2013). According to this view, developmental outcomes are linked to the

accumulation of adverse experiences, with increased risk for poor outcomes related to presence or absence of specific individual deviations from the expectable early social environment; for instance, threat versus deprivation (Rutter, 1979; Sameroff, 2000). Specificity and cumulative models have been linked to stress-response and allostatic load theories of how early social adversity impacts neurobiological development (Hanson et al., 2015; Nim Tottenham & Sheridan, 2010), whereby accelerated maturation in brain regions and circuitry that control emotion (e.g. amygdala, hippocampus, and PFC) is adaptive initially, but may have negative, cascading effects on subsequent brain development, increasing risk of developing various psychiatric and behavioural problems in later life (e.g. Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013).

In contrast, dimensional models emphasize that different mechanisms may lead to poor outcomes in the context of specific deviations in the early caregiving environment. However, most do acknowledge that the majority of early adverse environments probably involve a combination of factors to varying degrees, and therefore have both common and unique effects on development. One dimensional model is the ‘threat versus deprivation’ model (e.g. McLaughlin et al., 2021; McLaughlin & Sheridan, 2016), which separates early social adversity into two separate, but not mutually exclusive, factors. ‘Threat’ in this model reflects atypical experiences in the early social environment in terms of actual or threatened physical or emotional harm to the child from others, whereas ‘deprivation’ represents a lack of inputs from caregivers that are necessary for healthy socio-emotional and cognitive development (e.g. early institutional rearing which often involves a lack of both social and cognitive inputs). This model stresses the impact of early social deprivation on neural plasticity and related over-pruning of synaptic connections, reduced numbers of synaptic connections, and development in sensory cortices such as the fronto-parietal network (e.g. parietal connectivity with dlPFC). Early social threat is instead posited to have a greater impact on the development of brain regions linked to emotion and reward (e.g. amygdala, striatum, and ventromedial PFC) (Colich et al., 2020; McLaughlin et al., 2019).

Although less focused on much in the literature so far, other conceptual models highlight *unpredictability* in the context of early social adversity as an important risk factor for atypical neurocognitive development. In this case, social unpredictability could refer to instability in caregiver mood, as well as in presence or availability. It has been proposed that

lack of predictability in the early social environment also has profound effects on stress responsivity, which may lead to accelerated maturation in certain brain regions linked to emotion processing (Ellis et al., 2017; Liu & Fisher, 2022).

The main results presented in Chapters 3 and 4 do provide some support for dimensional models and the theory that poor cognitive outcomes (in this case, EF) are particularly likely in the context of early psychosocial deprivation. Furthermore, findings support the proposal that this is linked to the impact of deprivation on plasticity mechanisms, which leads to effects such as over-pruning of synapses and premature closing of plasticity periods in areas such as lateral PFC and fronto-parietal networks. However, results concerning fronto-striatal circuitry in Chapter 4 and from the wider project (presented in Appendix A) also suggest that both EF and emotion regulation are impacted negatively by peer-rearing in macaques, which is linked to development in limbic, salience, and cognitive control brain networks. While early psychosocial deprivation is characterized by a lack of socio-cognitive stimulation in the early caregiving environment, it can involve increased levels of threat, as well as elements of unpredictability. While effects on structural development in fronto-parietal brain regions and outcomes including increased ADHD symptoms may have been found more consistently after early institutionalization in humans (McLaughlin et al., 2019), many studies have also found effects of such early psychosocial deprivation on emotion regulation and associated brain networks, as well as increased risk for internalizing and externalizing disorders (e.g. Bos et al., 2011; Golm et al., 2020; Nelson et al., 2019; Sonuga-Barke et al., 2017). Notably, these disorders tend to involve problems in both EF and emotion regulation aspects of self-regulation.

More recently, a number of these models have been extended to incorporate the likely importance of striatal development. For example, dysregulation of the HPA-axis has been hypothesized to have profound effects on salience and reward processing via networks involving the striatum, amygdala, and PFC (e.g. Nim Tottenham, 2020; Nim Tottenham & Galván, 2016). A few have already demonstrated effects of early institutionalization on both functional (Fareri et al., 2017) and structural striatal connectivity (Bick et al., 2017). Fronto-striatal circuitry has an important role in the emergence of poor emotion regulation and EF (Eluvathingal et al., 2006; Fareri et al., 2017), and therefore may play a critical role in the emergence of poor self-regulation in the context of early psychosocial adversity. The results



presented in Chapter 4 and Appendix A support this proposal, with alterations in fronto-striatal structural connectivity linked to differences in EF and anxiety between rearing groups.

Although current conceptual models have been very useful for furthering our understanding on the effects of early social adversity, this section of the Discussion chapter highlights the fact that more complex models are now needed to better clarify the mechanisms through which different aspects of early adversity in terms of deviations in the expected social environment may lead to both overlapping and distinct developmental outcomes. Preliminary results concerning emotion regulation and potential interactions between cognitive and emotional aspects of self-regulation after psychosocial adversity will be discussed below.

## **Next steps for the current project**

Next steps for the work described here include looking at other measures of brain development, which will aid in developing a more comprehensive understanding of the neural mechanisms underlying poor EF linked to early psychosocial deprivation. First, analysis of other DTI metrics will be carried out, such as mean diffusivity (MD) in addition to fractional anisotropy (FA), and levels of myelination in different networks will be examined. This will provide more information about what may be driving changes in FA, and about the neural processes that could be leading to a premature closure of a sensitive period of brain plasticity during adolescence in the peer-reared group. Second, analyses of cortical surfaces will be conducted. Evidence suggests that cortical thickness and surface area follow different developmental trajectories and are inversely related to cognitive outcomes (e.g. Schnack et al., 2015). Third, analysis of the resting-state fMRI data, collected as part of the wider project and which reflects functional brain activity whilst not actively engaging in a task, will also offer insights into the functional organization of different brain networks, both in terms of typical and atypical development in macaques.

Another promising direction will be to conduct genetic analyses examining dopaminergic dysregulation, using the blood samples collected before MRI acquisition. Dopamine (DA) dysregulation in fronto-striatal circuits is proposed to play a crucial role in the emergence of cognitive difficulties after early psychosocial deprivation (Brett et al., 2015;

Mahmoodkhani et al., 2022; Smith & Pollak, 2020). Notably, imbalance of DA levels in the PFC can result in perseveration, while too much DA in the striatum can lead to distractibility and too much flexibility (Sajad et al., 2022). Previous investigations have explored the correlation between dopamine function, cortical activity, and task performance. The ideal balance between stability and flexibility of neural representation, which is critical for optimal performance, depends on the interaction of cortical D1 receptors and striatal D2 receptors (Nour et al., 2019). Different subtypes of dopamine receptors have divergent effects on working memory and learning, suggesting that while the impaired working memory performance seen in the context of psychiatric conditions such as schizophrenia may result from supra-optimal D2R signalling, non-pathological increases in D2R availability in healthy populations may be linked to improved performance (Gallo, 2019; Martel & Gatti McArthur, 2020; Nour et al., 2019). Results presented in Chapter 4 concerning an opposite pattern of association between fronto-striatal connectivity and EF in the two rearing groups, and with greater cortical thickness in vIPFC in peer-reared animals, could be in keeping with this.

Interestingly, the existence of different patterns in fronto-thalamic circuitry and dopamine signaling is associated with different pathologies involving EF deficits, including schizophrenia, bipolar disorder, mood disorders, and ADHD (Ashok et al., 2017; Mamah et al., 2019; Xia et al., 2012). Cortical thickness in PFC seems related to both the amount of dopamine release and to cognitive performance (Hettwer et al., 2022; Jaworska et al., 2017); in healthy individuals, thicker cortex is related to a smaller amount of dopamine release and better working memory (Casey et al., 2013; Cherkasova et al., 2017). This is in line with findings reported here in the mother-reared group, with thicker vIPFC predicting better working memory in this group. On the contrary, in individuals diagnosed with ADHD, thicker cortex has been associated with more dopamine release and poor EF in terms of more perseveration (Cherkasova et al., 2017). This is also in line with our results, with thicker vIPFC predicting worse inhibitory control and more random choices in the peer-reared group.

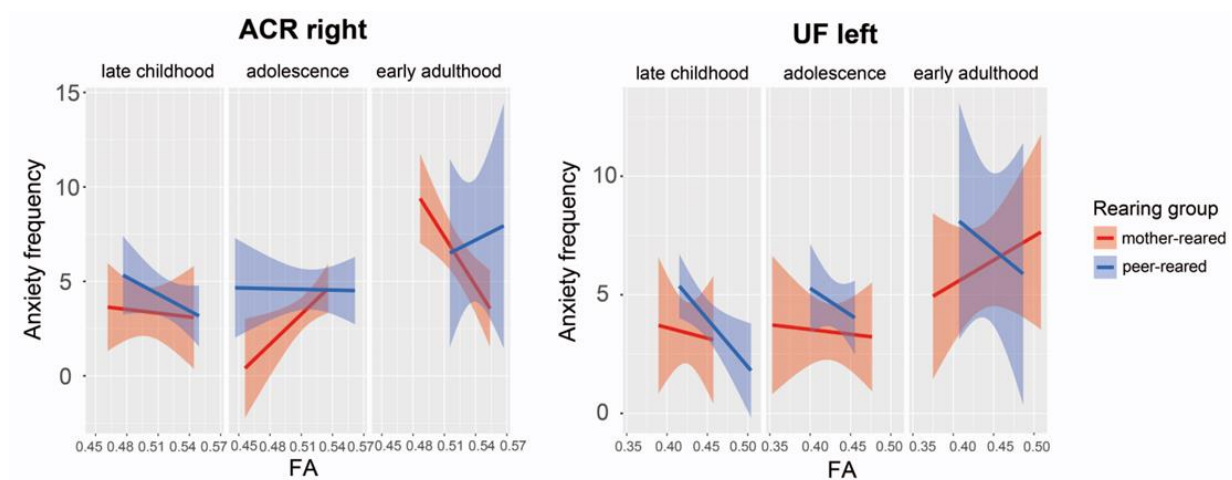
Based on such research looking at the dopaminergic system, and in accordance with previously discussed models of stress and plasticity, effects of early psychosocial deprivation on EF could relate to epigenetic dysregulation in dopamine signalling, with such adverse early experience leading to higher release in the PFC but not in the striatum. In fact, GABA regulation is also related to dopaminergic regulation. DA can directly modulate the physiology

of nonpyramidal, presumably GABAergic, neurons in the rat PFC (Zhou & Hablitz, 1999). Evidence suggests that D1 increases the excitability of interneurons, whereas D2 produces a decrease in GABA release in rat PFC (Seamans et al., 2001). Accordingly, a decrease in PFC GABA would affect dopamine signalling in an inverted U shape pattern (Lam et al., 2022; Tanaka, 2008). Higher release of DA and a higher Excitatory/Inhibition ratio in the PFC could be associated with the reduced thinning in vIPFC and increases in FA in fronto-striatal tracts across adolescence seen here in the peer-reared group. This may act as a compensatory mechanism in very early development. However, it is important to note that other cortical and subcortical regions are likely involved (e.g. parietal, limbic). Further research is necessary to fully comprehend the relationship between various aspects of dopamine function and its role in poor executive function in the context of early psychosocial deprivation in human and nonhuman primates.

Examination of how both cognitive and emotional aspects of self-regulation predict poor outcomes, including increased risk for anxiety and ADHD-like symptoms, will also be a critical next stage of the wider research project described in this thesis. In Appendix A, preliminary results concerning emotion regulation and anxiety are presented. In a published paper (Rayson et al., 2021), we found that peer-reared animals demonstrate an elevated attention-bias toward threat in pre-adolescence, with greater bias linked to more anxiety-like behaviour. This suggests that poor emotion regulation strategies might increase the risk for anxiety in this group. Indeed, the peer-reared group were found to have higher levels of anxiety at all three project time-points (i.e. late childhood, adolescence, early adulthood), as well as greater emotional reactivity to social threat, which predicted anxiety in adulthood. In Appendix A, we also show that early psychosocial deprivation has an effect on the development of fronto-limbic white matter tracts; in the peer-reared group, higher FA was found during adolescence in the superior cingulum (SC) and in the fornix during late childhood. This is not in line with findings in human children, with decreased integrity in these tracts having been related to internalizing problems in the context of early institutionalization (Bick & Nelson, 2015). However, this may be linked to the age of assessment in the different studies. For example, there is some evidence for more variability in associations between white-matter integrity and emotion regulation during adolescence, such as increased irritability (Hodgdon et al., 2022). Higher FA in related networks has also been interpreted in terms of adaptive

reorganization in macaques, with increased structural integrity in the context of social adversity representing a compensatory mechanism to help cope in the current environment (Howell et al., 2019).

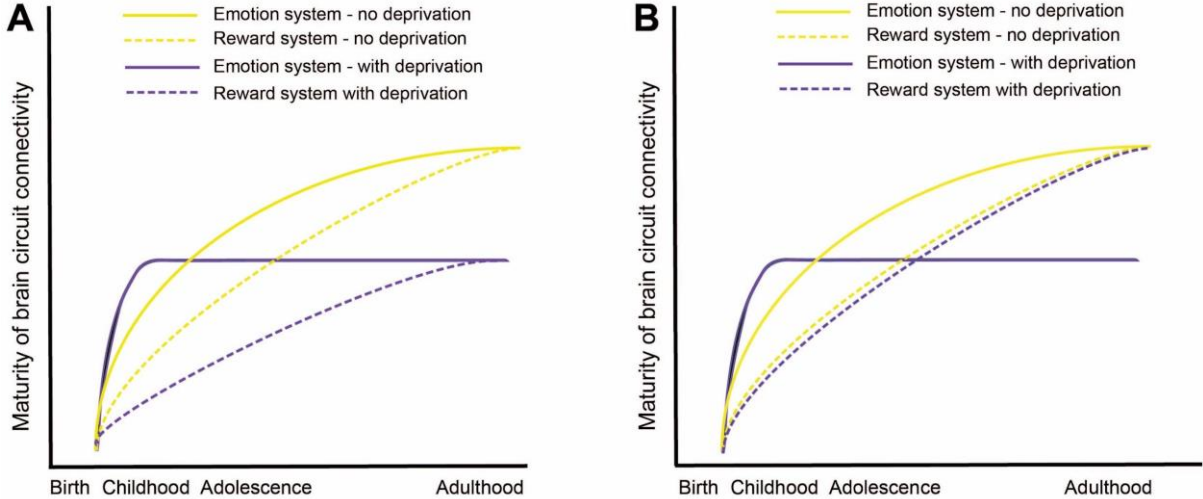
Rearing group also modulated the relationships between white matter integrity and anxiety in both the fronto-limbic and fronto-striatal tracts (Appendix A). In the mother-reared group, higher integrity in the right anterior corona radiata (ACR) predicted less anxiety in late childhood and early adulthood. However, in the peer-reared group, this relationship was only present earlier on in development, with a positive relationship perhaps emerging by adulthood (Figure 5). Integrity in this tract has been linked to several psychopathologies that involve emotion dysregulation (e.g. Karababa et al., 2015; Sanjuan et al., 2013). This result is in accordance with higher integrity predicting positive outcomes in terms of EF in the mother-reared group (Chapter 4), and perhaps supports the proposal that while effects of early deprivation on certain neural changes are adaptive earlier on, they can later lead to increased risk for poor outcomes such as anxiety later on.



**Figure 5.** Relationships between FA, rearing group, and anxiety in fronto-striatal and fronto-limbic white matter ROIs. Greater integrity in the left uncinate fasciculus (UF; right image) predicted less anxiety at the first two time-points, but a stronger relationship in peer-reared animals across all time-points. Greater integrity in the right anterior corona radiata (ACR; left image) in mother-reared group predicted less anxiety in childhood and early adulthood, but more anxiety in adolescence; while in peer-reared group greater integrity in the right ACR predicted less anxiety in childhood and adolescence, but not in early adulthood. Error bars represent +/- SE.

Interestingly, in the left uncinate fasciculus (UF), which is the main white matter tract connecting the amygdala with PFC, a negative relationship between FA and anxiety was stronger in the peer-reared group across time, even though this relationship became weaker

over time in general (Figure 5). This aligns with previous literature showing that in typical development, a relationship between UF integrity and anxiety weakens with age (Hein et al., 2018), perhaps reflecting typical refinement in circuits regulating emotion. It is possible that in our peer-reared group, maintenance of this relationship serves a protective mechanism; furthermore, whether this reflects accelerated or delayed development, this could lead to negative outcomes later on, having cascading effects on subsequent brain development such as in fronto-striatal circuitry. As noted previously, a compensatory mechanism involving fronto-striatal circuits may enhance working memory in the peer-reared group, as evidenced by higher integrity in the ALIC (Chapter 4), but may also impair inhibitory control, working-memory decay, and related emotion regulation. The idea of a ‘developmental trade-off’ between accelerated development in circuitry related to emotion versus that to reward and motivation processing is a relatively new one in the literature, but it is gaining support. Herzberg and Gunnar (2020) make an interesting proposal in terms of functional brain connectivity, whereby in the context of early life stress, accelerated development in emotion brain circuitry (e.g. fronto-amygdala connectivity), which may reach maturity by late childhood, comes at the cost of development in reward-related circuitry across development into adulthood (Figure 6). This could have particularly profound effects during adolescence, and fits with our findings in terms of stability in the integrity of certain white matter tracts linked to emotion regulation and their relationship with anxiety in the peer-reared group (e.g. UF; Appendix A), but the changes seen over time in the relationship between integrity in fronto-striatal tracts and both EF and anxiety (Chapter 4 and Appendix A).



**Figure 6.** *Conceptual illustration of a developmental trade-off associated with accelerated brain maturation in the emotion processing versus reward system following early psychosocial deprivation (A). This is compared to no developmental trade-off between the two systems (B). Most studies examining neural development after early social adversity have focused on development of emotional brain networks; limited research has looked at development of other systems and their interactions. However, behavioural studies focused on effects of various forms of early social adversity suggest this is also linked to atypical processing of reward-related information. It may be that accelerated maturation of emotion-related brain circuitry comes at the cost of development in circuitry linked to reward processing, motivation, and decision-making. Evidence in support of this is increasing, with a number of studies now showing that early institutionalization is associated with alterations in the development of striatal circuitry. This figure was adapted from Herzberg & Gunnar (2020), in which a potential trade-off between functional connectivity in emotion and reward systems after early life stress is proposed.*

Furthermore, next steps for this project will involve looking at how emotional and cognitive processes interact to predict poor outcomes in the context of early psychosocial adversity. For example, attention biases and working memory may aid in the detection of threats and exploitation of rare opportunities in chaotic environments. This is supported by the attention bias results presented in Appendix A and the EF results. However, these benefits may come at the expense of processes such as inhibitory control and performance in tasks requiring long-term storage and retention in the presence of distractions (Ellis et al., 2022; Mittal et al., 2015; Young et al., 2018, 2022). Therefore, together, the negative impact of early social adversity on the interaction between cognitive and emotional processes likely contributes to emotion dysregulation, and thus an increased risk for poor outcomes such as anxiety disorders. This increased risk is also supported by results presented in Appendix A, showing that as well as poor EF and emotion dysregulation, anxiety is greater in peer-reared animals.

Investigating the neural substrates that might mediate a relationship between EF and emotion processing will help us to gain a deeper insight into the mechanisms underpinning risks for outcomes including anxiety disorders and ADHD after early psychosocial deprivation. As noted before, GABAergic dysregulation can occur in both the PFC and the amygdala, which could lead to abnormal fronto-amygdala connectivity (Guadagno et al., 2021). An Excitatory/Inhibition imbalance could then lead to accelerated development in this circuitry, perhaps serving a protective role early on but also less flexibility later related to the early closure of sensitive periods of brain development. Since the PFC is one of the last brain regions to reach maturity, as well as its protracted development of connectivity with regions such as

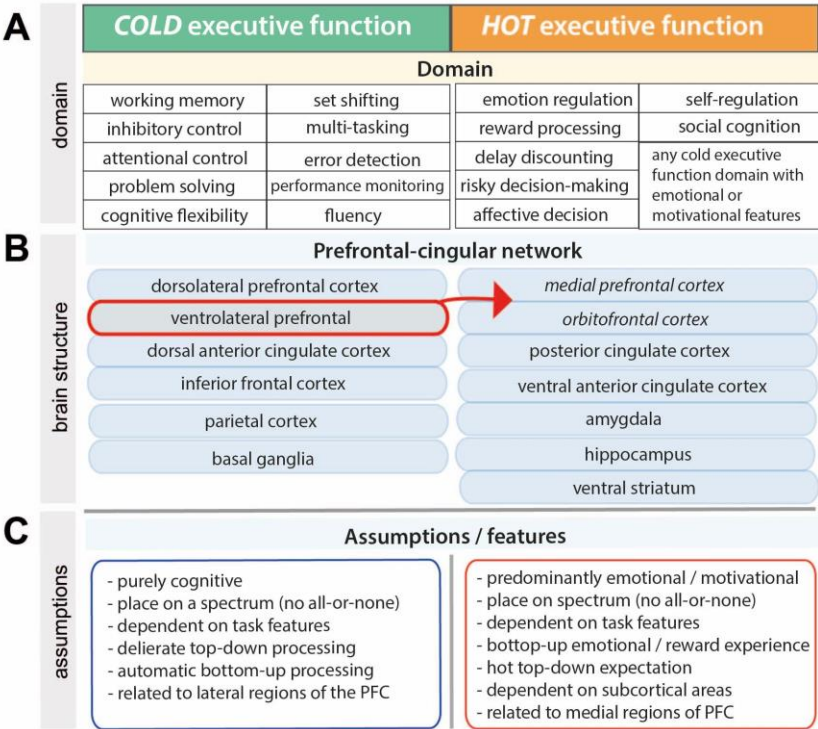
the striatum, the closing of plasticity windows prior to adolescence, despite being adaptive at first (Adam et al., 2021), can likely have profoundly negative effects of brain development thereafter.

Relatedly, it is becoming increasingly common in the field to separate EF into emotional ('hot') versus cognitive ('cold') processes, with all EFs posited to exist along a spectrum whereby they are 'hotter' or 'colder' based on the context (e.g. the presence or absence of emotional stimuli). In this sense, emotion regulation is considered an executive function, which involves components such as inhibition and working memory in emotional contexts. In a recent review paper (Salehinejad et al., 2021), a prefrontal-cingular network is proposed to underlie both hot and cold EFs, with the lateral PFC (dlPFC and vlPFC) and dorsal anterior cingulate cortex (dACC) related more strongly to cold EFs, and the posterior cingulate cortex (PCC), medial and orbital PFC, the ventral ACC (vACC), and limbic structures such as the amygdala, hippocampus and ventral striatum more strongly related to hot EFs. Importantly, the vlPFC is also connected to medial and orbital PFC, potentially providing a convergence point for interaction between the hot and cold streams (Trambaiolli et al., 2022).

The conceptualization of EF as comprising a hot-cold spectrum has been applied to theories concerning poor EF observed in the context of various psychiatric and neurodevelopmental disorders associated with early psychosocial deprivation, including anxiety disorders and symptoms of ADHD and ASD. In the case of anxiety disorders, for instance, anxiety has been linked to impaired inhibition and attention biases (i.e. cold EFs), but which are dependent on the presence of threat-related stimuli or cognitive load (Leonard & Abramovitch, 2019). Alterations in both the structure and function of brain regions implicated in both hot and cold streams of the prefrontal-cingular network suggested to underlie EF (Salehinejad et al., 2021) have been associated with anxiety, including

hyperactivation of medial PFC and ventral ACC (hot stream), and hypoactivation of dlPFC and dACC (cold stream), which are also linked to amygdala hypersensitivity (Vicario et al., 2019).

**Figure 7.** Model of hot and cold executive functions and their potential underlying brain networks. Illustrated here are the different domains included in hot versus cold functions (A), the brain structures



thought to be implicated in these functions, with vlPFC perhaps serving as integration hub (B), and the assumptions and features linked to hot and cold EF streams (C). This figure was adapted from Salehinejad et al. (2021).

Results presented in Chapter 4 and appendices A and B lend support to this theory, suggesting that the negative effects of early deprivation on EF, emotion regulation, and anxiety risk, as well as differences in structural development of PFC (i.e. cortical thickness in dlPFC and vlPFC) and its connectivity with limbic and striatal regions (e.g. white matter integrity in the UF, fornix, ACR and ALIC), may be related to both cold and hot EFs, depending on the context (Figure 7). This is an interesting avenue that will be investigated using data from the current project.



## Future directions in the research field

In general, future research on the impact of early social adversity on development should aim to elucidate the specific learning mechanisms through which psychosocial deprivation leads to poor outcomes. Associative learning and reinforcement learning mechanisms, for example, have been proposed to affect both socio-cognitive and behavioural development in this context, including how reward processing could interact with and/or affect self-regulation. According to associative learning theory (Gallistel & Matzel, 2013), the brain adjusts itself to the experienced world without fully comprehending the underlying causes of improved performance. Reinforcement learning theory, derived from Hebb's work, posits that long-lasting learning derives from incrementally reinforced and rewarding actions through accumulated experience (Doya, 2007; Triche et al., 2022).

We know that social experiences in the early years play a crucial role in shaping an individual's ability to process information from their environment, including social information (Pirazzoli et al., 2022; Wade et al., 2022b). Social information processing theory (Dodge & Crick, 1990) suggests that children with disruptive behaviour problems often perceive, interpret, and make decisions about social information in ways that increase the likelihood of aggressive behaviour. These difficulties could stem from issues with attachment or the presence of coercive cycles in the family environment (Martel, 2019; Smith et al., 2014). Social information processing models have been established for several mental disorders, including depression, aggression, anxiety disorders, oppositional defiant disorder, and schizophrenia (Dillon et al., 2020; Lau & Waters, 2016; Martel, 2019). In the context of early social adversity, attention biases towards threat have been found, which increase the risk for anxiety (Crick & Dodge, 1994; Rayson et al., 2021; Sheridan et al., 2018; Troller-Renfree et al., 2017). These information processing biases, which result in an over-identification of situations as threatening, may serve a protective function in hazardous environments, but are also linked to internalizing and externalizing problems later on (Morales et al., 2016). Research comparing anxious and non-anxious parents suggests that disruptions in associative learning could be a critical mechanism by which social adversity increases the risk of such problems (Sheridan et al., 2018). In view of these findings, it has been proposed that difficulties in social information processing and changes in emotional processing are two core mechanisms linking threat

exposure and negative mental health outcomes in children and youth (McLaughlin, 2020; Wade et al., 2022).

Reinforcement learning is fundamentally linked to reward processing. Maternal separation and subsequent food insecurity have been associated with poor reward performance, as well as lower fronto-striatal white matter integrity that mediates an association between food insecurity and depressive symptoms (Dennison et al., 2019). Multiple human studies focused on effects of early psychosocial deprivation in human and non-human samples suggest that such deprivation leads to decreased responsiveness to reward, or an inability to use, feedback and reward-related cues and related brain networks (Herzberg & Gunnar, 2020; Hodel et al., 2015; Merz et al., 2016; Sheridan et al., 2018; Sheridan et al., 2012). Changes in these motivation-related behaviours appear to be founded on a host of neurobiological changes, including lower functional activity in the ventral striatum, altered glutamatergic signalling, changes in dopaminergic modulation, and altered molecular signatures of brain plasticity that may be regulated by epigenetic mechanisms, along with more wide-spread circuits such as fronto-striatal network (Goff et al., 2013; Hanson & Nacewicz, 2021; Herzberg & Gunnar, 2020). In Chapter 3, we did test versions of the computational model which included reinforcement learning of choice value as a factor, but none of these models best explained the performance in both groups. However, we cannot exclude the possibility that this process could have an important role in the negative outcomes seen in the context of early social adversity. In addition, a few recent studies suggest that, as well as reinforcement learning, negative reinforcement or ‘punishment’ learning should be taken into account (Humphreys et al., 2016; Liebenow et al., 2022). More research is investigating how these different proposed learning mechanisms are impacted in the case of early social adversity is now needed, with multiple mechanisms at distinct and overlapping stages of development probably playing an important role in various poor outcomes.

## **Strengths and limitations of the current research**

The research presented in this thesis possesses several strengths. First was the use of a longitudinal experimental design to track neural and behavioural development across adolescence. This type of design enables examination of the dynamic and evolving nature of

the relationship between brain and behaviour across a time of increased vulnerability for poor outcomes often associated with early psychosocial deprivation. Second, the use of objective measures of behaviour to assess cognitive and emotional development is an important advantage compared to the majority of human research in the context of early social adversity, where questionnaires completed by caregivers, teachers, or participants themselves are often used in isolation. The observational approaches used here minimize the potential for the bias inherent to such self- or other-reported measures. Third, the multidisciplinary approach adopted here is a key strength, combining various techniques such as magnetic resonance imaging (MRI), behavioural assessment, and computational modelling for a more thorough exploration of the neurocognitive mechanisms underlying the association between early psychosocial adversity and self-regulation. Finally, meticulous control of early rearing conditions was achievable via the use of a nonhuman primate model, resulting in reduced variability in both the timing and duration of early psychosocial experiences. These factors play a significant role in determining later behavioural and neurological outcomes (Fox et al., 2011; Gee & Casey, 2015; Hodel et al., 2015), and therefore are important to account for.

However, there are also some limitations to the current project that need to be acknowledged. One of these is the relatively small sample size, which restricts the generalizability of findings to larger populations, and may have reduced power to identify meaningful higher-order effects. Another limitation is the lack of assessments at ages prior to late childhood and after early adulthood, which limits understanding of the trajectories of neurocognitive development from the time of initial caregiver deprivation and across later life. Finally, although these results further our knowledge on the neurocognitive mechanisms that likely underlie poor outcomes in the context of early psychosocial deprivation, they do not reveal anything about the specific learning mechanisms through which alterations in development occur, or how learning trajectories may differ after different types of early social adversity. All these limitations must be addressed in future research to more fully elucidate how early social adversity impacts neurocognitive development and the risk for long-term poor outcomes in different domains.

## Conclusion

To conclude, findings presented in this thesis provide novel and important insights into the effects of early psychosocial deprivation on self-regulation and its neural bases across adolescence. The main results suggest that early deprivation in macaques leads to impairments in executive function that persist into adulthood. These impairments are related to both structural development of the prefrontal cortex, and connectivity within fronto-parietal and fronto-striatal brain circuitry. These findings also provide some support for a compensatory mechanism emerging after early psychosocial deprivation, in terms of changes in structural brain development. Additionally, results in Appendix A indicate that emotion dysregulation persists into adulthood after early psychosocial deprivation in macaques, which is also associated with an increased risk for anxiety; this relationship is modulated by structural brain connectivity in networks linked to emotion processing and regulation. Further research, including longitudinal studies across more stages of development (e.g. infancy, childhood, adolescence, and adulthood), is now necessary to more fully map the emergence of various developmental trajectories of self-regulation after different forms of adversity, as well as the learning mechanisms that may contribute to healthy versus pathological development. This will be essential for the future design of treatments and interventions to ameliorate and prevent poor outcomes in the context of early social adversity, and thus improve the quality of life of affected individuals.

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## **APPENDIX A.**

### **Early psychosocial deprivation, emotion processing, and anxiety risk**

## **Affect-biased attention and anxiety in the context of early psychosocial deprivation**

*Rayson, H., Massera, A., Belluardo, M., Ben Hamed, S., & Ferrari, P. F. (2021). Early social adversity modulates the relation between attention biases and socioemotional behaviour in juvenile macaques. Scientific reports, 11(1), 1-11.*

In this paper we looked at how early psychosocial deprivation influences affect-biased attention and relates to anxiety at the first project time-point (2.5 years). Affect-biased attention is thought to play a fundamental role in early socioemotional development (e.g. prosocial behaviour and risk for anxiety disorders), but factors influencing its emergence are unclear, as are associations with typical versus pathological outcomes (Morales et al., 2016). Atypical affect-biased attention is demonstrated by children exposed to early institutional rearing (Troller-Renfree et al., 2015; 2017), and may reflect an important aspect of emotion dysregulation increasing the risk for mood disorders and antisocial behaviour in individuals exposed to early psychosocial deprivation. Like early institutionalization in humans, peer-rearing in macaques has been associated with increased anxiety-like behaviour (e.g. Dettmer et al., 2012), though whether this is linked to affect-biased attention was previously unexplored.

In this study, we aimed to: a) establish whether pre-adolescent macaques demonstrate attention biases to both threatening and reward-related dynamic facial gestures; b) examine the effects of early deprivation on such biases; and c) investigate how this relation may be linked to socioemotional functioning (anxiety and social engagement). We presented our two groups of macaques (mother-reared/peer-reared) with pairs of dynamic facial gestures comprising two conditions: neutral-threat and neutral-lip-smacking. Note, lip-smacking is an affiliative facial gesture in macaques. Attention biases to threat and lip-smacking were calculated as the proportion of gaze to the affective versus neutral gesture. Measures of anxiety and social engagement (i.e. social grooming) were also acquired from videos of the subjects in their everyday social environment over a number of weeks.

Results revealed that while both groups demonstrated an attention bias towards threatening facial gestures, a greater bias linked to anxiety was demonstrated by the peer-reared group only. Only the mother-reared group demonstrated a significant attention bias

towards lipsmacking, and the degree of this positive bias was related to duration and frequency of social engagement. Such results suggest that early psychosocial deprivation does indeed impact affect-biased attention in macaques, and that threat biased attention is linked to increased anxiety in this early rearing context. These findings offer important insights into the effects of early social experience on affect-biased attention and related socioemotional behaviour in nonhuman primates, and demonstrate the utility of this model for future investigations into the neurocognitive mechanisms underlying these relationships across development. The full paper (Rayson et al., 2021) is included in pages 252-285 of this Appendix.

## **Longitudinal relationships between deprivation, structural brain connectivity, and anxiety**

We are currently running analyses to look at whether structural brain connectivity in fronto-limbic and fronto-striatal tracts modulate a relationship between early psychosocial deprivation and anxiety over time, as well as how emotional reactivity modulates these relationships. This brain circuitry is implicated in anxiety disorders (Kenwood et al., 2015) and is affected by early institutionalization and related internalizing symptoms in late childhood (Bick et al., 2015;2017).

Detailed information and results are presented on pages 286-296 of this Appendix, but briefly, preliminary analyses reveal that: i) anxiety-like behaviour is more frequent in the peer-reared versus mother-reared group across time; ii) emotional reactivity is greater in the peer-reared versus mother-reared group over time and is related to anxiety at the 5 year time-point; iii) year/group ROI diffs...; and iv) there are differing relationships between white matter integrity in specific tracts and rearing group/reactivity that predict anxiety over time.

The MRI/DTI work presented here was led by Dr. Bassem Hiba and his team; Hind Errame, who is supervised by Dr. Hiba, with the help of Nathalie Richard and Yann Bihan-Poudec, completed all preprocessing of the MRI data. Thanks also to Suliann Ben Hamed, Mathilda Froesel and Maeva Gacoin for their help with the acquisition of the MRI data.

**Published manuscript (accepted version)**

**Early social adversity modulates the relation between attention biases and socioemotional behaviour in juvenile macaques**

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## ***Abstract***

Affect-biased attention may play a fundamental role in early socioemotional development, but factors influencing its emergence and associations with typical versus pathological outcomes remain unclear. Here, we adopted a nonhuman primate model of early social adversity (ESA) to: i) establish whether juvenile, pre-adolescent macaques demonstrate attention biases to both threatening and reward-related dynamic facial gestures; ii) examine the effects of early social experience on such biases; and iii) investigate how this relation may be linked to socioemotional behaviour. Two groups of juvenile macaques (ESA exposed and non-ESA exposed) were presented with pairs of dynamic facial gestures comprising two conditions: neutral-threat and neutral-lipsmacking. Attention biases to threat and lip-smacking were calculated as the proportion of gaze to the affective versus neutral gesture. Measures of anxiety and social engagement were also acquired from videos of the subjects in their everyday social environment. Results revealed that while both groups demonstrated an attention bias towards threatening facial gestures, a greater bias linked to anxiety was demonstrated by the ESA group only. Only the non-ESA group demonstrated a significant attention bias towards lipsmacking, and the degree of this positive bias was related to duration and frequency of social engagement in this group. These findings offer important insights into the effects of early social experience on affect-biased attention and related socioemotional behaviour in nonhuman primates, and demonstrate the utility of this model for future investigations into the neural and learning mechanisms underlying this relationship across development.

## ***Introduction***

In the face of limited perceptual and cognitive resources, attention mechanisms enable the brain to manage competing demands in the everyday environment by prioritizing a subset of stimuli for dedicated processing. Such mechanisms guide behaviour from the earliest months postpartum, serving as a fundamental base for learning, self-regulation, and memory (Buss et al., 2018; Rueda et al., 2005). *Affect-biased* attention specifically is posited to play a broad and pervasive role in early socioemotional development (Morales et al., 2016; Todd et al., 2012), with emerging affect biases shaping an infant's experience of their environment via preferential processing of threat- and reward-related information. This, in turn, is thought to support the emergence of adaptive approach and avoidance behaviour (Peltola et al., 2013, 2015). However, specific affect-biases have also been linked to poor socioemotional functioning later on in development (e.g. Pérez-Edgar et al., 2010; Roy et al., 2008), and many questions remain concerning the mechanisms through which affect-biased attention arises and may relate to both typical and pathological outcomes.

Biased attention towards threat-relevant information serves an essential survival function (Pourtois et al., 2013). It is unsurprising, therefore, that most affect-bias studies have focused on threatening stimuli such as angry or fearful versus neutral faces. An attention bias to threat (ABT) emerges during the first year postpartum (Morales et al., 2017; Peltola et al., 2013), and has been linked to positive socioemotional outcomes in the form of secure infant attachment (Peltola et al., 2015). Conversely, ABT has also been associated with emotion regulation difficulties, social withdrawal, and anxiety in both adults and younger populations (Bar-Haim et al., 2007; Dudeney et al., 2015), with cognitive models of anxiety attributing a causal relation to ABT in the development and or maintenance of anxiety (Beck & Clark, 1997; MacLeod & Mathews, 2012; Mathews & MacLeod, 2002). This apparent contradiction suggests that any increased vulnerability conferred by threat-biased attention may arise from an early-emerging, normative threat bias (Field and Lester 2010; Dodd et al., 2015), with excessive ABT or a failure to inhibit ABT exacerbating the risk for psychopathology (Kindt & Van Hout, 2001). Inconsistent findings concerning a link between ABT and anxiety in childhood, with no relation often found despite ABT presence (e.g. Dodd et al., 2015), is in keeping with this idea, but so far, very little is known about how ABT and socioemotional function interact across development.



An attention bias to positive stimuli (ABP) such as happy faces may also play an important role in early socioemotional functioning. Such positive biases are often conceptualized as a bias towards rewarding stimuli (Morales et al., 2016). Relatively little is known about the emergence of ABP, but evidence suggests this also arises at an early stage in development (Burriss et al., 2017; Morales et al., 2017). ABP has been associated with several aspects of positive socioemotional functioning in children and adults, including social engagement and prosocial behaviour (Troller-Renfree et al., 2015), adaptive emotion regulation skills (Joormann & Gotlib, 2007), and positive affect (Grafton et al., 2012). Notably, ABP has also been linked to lower levels of anxiety (e.g. Taylor et al., 2011), and may act as a protective factor in developmental populations at increased risk for poor socioemotional outcomes. This includes risk for anxiety and internalizing problems in behaviourally inhibited and previously institutionalized children (Dodd et al., 2020; Troller-Renfree et al., 2015, 2017; VanTieghem et al., 2017). Nevertheless, findings linking ABP to anxiety in younger populations are again mixed, with some studies failing to find any relation between ABP and anxiety in childhood (Roy et al., 2008; Waters et al., 2010).

Nonhuman primate (NHP) models could add significantly to our understanding of affect-biased attention and its role in early socioemotional functioning. Adopting a comparative developmental approach can provide unique insights into the origins of human cognition, highlighting similarities and divergences in our evolutionary history (Rosati et al., 2014, 2018). However, it is currently unclear whether affect biases comparable to those in humans are present in early NHP development, and how these may relate to other specific developmental outcomes. Rhesus macaque (*Macaca mulatta*) monkeys are very similar to humans in terms of cognition, socio-affective characteristics, and brain organization, and are thus commonly utilized to investigate the aetiology of various psychiatric and neurodevelopmental disorders, including anxiety (see Coleman & Pierre, 2014; Kalin & Shelton, 2003). Macaques also live in large social groups, have an extended period of development comprising distinct infant, juvenile (pre-adolescent and adolescent), and adult periods, and the early macaque mother-infant relationship shares many commonalities with humans (Ferrari et al., 2009). The macaque model is, therefore, especially well-suited to developmental studies, and could provide particularly valuable information concerning the mechanisms underlying ABT and ABP emergence. Accordingly, we adopted a macaque model

in the current study with the goal of furthering our understanding of affect-biased attention in NHPs, and investigating the suitability of this as a translational model of its development and related socioemotional outcomes.

Early-emerging ABT also appears normative in macaques, assessed via presentation of threatening versus neutral faces (Mandalaywala et al., 2014; Morin et al., 2019; Rosati et al., 2018). To our knowledge, only one macaque study has investigated ABP specifically, with no bias towards a positive, affiliative facial gesture ('lip-smacking') versus a neutral face revealed at any stage in development (Rosati et al., 2018). Nevertheless, this lack of bias may have resulted from difficulty in discriminating between the two static images, as lip-smacking, a highly rhythmic and dynamic facial gesture, is very difficult to portray in a static stimulus. To date, the majority of both human and NHP studies that have utilized paired affective vs. neutral facial stimuli to investigate affect-biased attention have used static images. The use of dynamic facial stimuli, however, improves various aspects of perception and enhances attention biases in human adults (Ambadar et al., 2005; Cadek et al., 2017; Kamachi et al., 2013), and recruits dissociable neural pathways from those involved in the perception of static faces (Kilts et al., 2003; Pitcher et al., 2014). This issue of static versus moving faces is especially pertinent for developmental research. Dynamic stimuli can enhance neural and behavioural discrimination of emotional versus neutral faces from early infancy (Ichikawa et al., 2014; Quadrelli et al., 2019), and attention to emotional expressions is modulated by stimulus motion across childhood, adolescence, and into adulthood (Nelson & Mondloch, 2018). Altogether, this highlights the importance of adopting more ecologically valid, dynamic facial stimuli in studies of affect-biased attention, and indeed, there is a growing movement within the wider research community towards the use of more naturalistic stimuli in studies of social attention with humans and NHPs (see Fan et al., 2021).

To address outstanding questions concerning the mechanisms through which affect-biased attention emerges and relates to both typical and atypical functioning, it is critical to consider which factors may contribute to individual differences in ABT and ABP, and how such differences may confer vulnerability or resilience. It is well established that early social adversity can increase risk for a number of adverse socioemotional outcomes, including anxiety and reduced social engagement in humans and macaques (e.g. Almas et al., 2015; Dettmer et al., 2012; McGoron et al., 2012; Winslow et al., 2003). A small number of studies

have linked elevated ABT specifically to early social deprivation (Troller-Renfree et al., 2015, 2017) and maternal anxiety (Morales et al., 2017) in children and human infants, with maternal abuse and over-protectiveness associated with ABT magnitude in infant and adolescent macaques (Mandalaywala et al., 2014; Morin et al., 2019). Early social deprivation may also impact ABP, with ‘care-as-usual’ versus foster home placement related to a reduced or absent bias towards happy faces (Troller-Renfree et al., 2015, 2017), and greater ABP to more social engagement and fewer internalizing problems (Troller-Renfree et al., 2015, 2017) in the context of early institutionalization. It remains unknown whether early social adversity has similar effects on the relation between affect-biased attention and comparable socioemotional outcomes in NHPs.

The current study was designed to investigate both ABT and ABP in pre-adolescent macaques using dynamic facial stimuli, and to examine whether such biases are linked to socioemotional functioning; specifically, anxiety-like behaviour and social engagement. To consider the effects of early social adversity, we assessed two groups of juvenile macaques (aged 2.5 years), one mother-reared and one peer-reared. Peer-rearing is often adopted in macaque models of early social adversity, and has been associated with both increased anxiety and decreased social behaviour (Dettmer et al., 2012; Winslow et al., 2003). Our hypotheses were: i) although all animals will demonstrate attention biases, peer-reared animals will demonstrate greater ABT, and mother-reared animals will demonstrate greater ABP; ii) greater ABT will be related to more anxiety-like behaviour, but greater ABP will be related to less; and iii) greater ABP will be related to more social engagement.

## **Methods**

### **Subjects and housing conditions**

The sample consisted of 21 juvenile rhesus macaques (*Macaca mulatta*), 11 mother-reared (six female) and 10 peer-reared (five female). Subjects were aged around 2.5 years at the time of this study (mother-reared; M = 943.18 days, SD = 17.98; peer-reared; M = 956.2 days, SD = 20.24). Subjects were housed at the *Institut des Sciences Cognitives Marc Jeannerod* (ISC-MJ), CNRS, in mixed mother- and peer-reared social groups of 5-6 animals. All housing and procedures conformed to current guidelines concerning the care and use of laboratory animals (European Community Council Directive No. 86–609), and were approved by our local ethics board, ‘Comité d’Ethique Lyonnais pour les Neurosciences Expérimentales’ (CELYNE)

C2EA #42 (03.10.18), and the French Ministry of Research (10.10.18); project reference APAFIS#15091\_2018071014483295\_v2. All reporting here conforms to the recommendations in the ARRIVE Guidelines for Reporting Animal Research.

All subjects were born and raised at the Laboratory of Comparative Ethology at the National Institutes of Health, US. Peer-reared animals were raised in a nursery with access to same-aged peers; see Shannon et al. (1998) for more rearing protocol details. Rearing procedures were approved by the NICHD and the University of Maryland Animal Care and Use Committee, and adhered to the NIH Guide for the Care and Use of Laboratory Animals. Animals were relocated to the Rousset Primatological Station, CNRS, France at two years of age. More information about the rearing protocol and housing can be found in the SI.

### **Facial gesture stimuli**

Stimuli for the gaze bias task consisted of short, dynamic video clips (5s) of an unfamiliar adult female macaque performing three types of facial movements: i) neutral facial movements (i.e. no gesture but with small movements of, for example, the nose and mouth); ii) lip-smacking (LPS), comprised of the rapid, rhythmic opening and closing of the mouth, and pursing of the lips; and iii) open-mouth threat, comprised of the wide opening of the mouth and lowering of the jaw, with lips held in a tense position covering the teeth. The onset and duration of movement, size, brightness, contrast, spatial frequency, and overall motion levels were controlled for (see SI) to ensure that neutral, lip-smacking, and threat video stimuli did not differ in terms of low-level visual features. All videos started with a 500ms static period showing the first frame of the video (with a neutral facial expression), followed by 4500ms of movement (i.e. two consecutive instances of each gesture or neutral movement sequence).

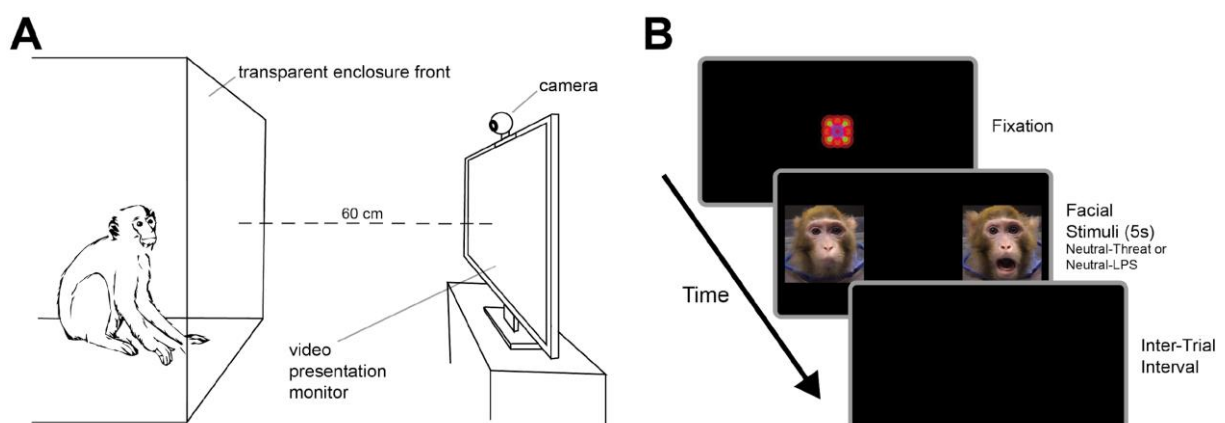
### **Gaze bias task**

Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; 87 × 100 × 120cm enclosure with a clear panelled front. Before commencing the task, a widescreen computer monitor (35 × 61cm; 2560 × 1440 resolution) was placed 60cm from the front of the enclosure, and animals were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure and presentation of non-

social video stimuli before the day of assessment. Animals were recorded during the task using a webcam (30fps) placed on the top-centre of the monitor.

Animals were presented with pairs of neutral-affective gesture stimuli comprising two conditions: i) Neutral-Threat (five trials per subject); and ii) Neutral-LPS (five trials per subject), i.e. the positive or reward condition. Video pairs were presented for 5s per trial, with condition order and position (left or right) of neutral-affective gesture videos counterbalanced across subjects. Before the stimuli appeared, a moving geometric pattern accompanied by a non-social sound was presented in the centre of the screen to attract the subject's attention, with stimuli presentation then triggered by an experimenter watching the animal live on a separate monitor (not in view of the subject). Additionally, a calibration procedure was conducted before presentation of experimental stimuli, whereby images of objects (e.g. ball, toy car) were presented on the right, centre, and left of the screen. Each image was jittered up and down slightly to attract attention and was accompanied by a non-social sound. Psychopy v1.90.2 (Peirce et al., 2019) was used for stimulus (calibration and experimental) presentation, with video recording onset and offset automatically triggered at the start and end of each presentation. This sequence and the experimental set-up is illustrated in Fig. 1.

Subjects' gaze (left, right, other, offscreen) was manually coded offline, frame-by-frame, by a researcher blind to the condition being presented and the position of the neutral-gesture stimuli. A random 15% of videos were coded by a second researcher to establish reliability, with very good reliability scores obtained ( $\kappa = 0.84$ ).



**Figure 1.** A) Schematic illustration of the gaze bias task set-up; B) Illustration of a trial in the gaze bias task. An experimenter triggered the appearance of fixation and facial stimuli screens when the subject looked towards the monitor.

### **Behavioural observation**

Video recordings of the social group (50fps) were made two times per week, once in the morning and once in the afternoon, for three weeks. Two cameras were used to capture the whole home enclosure and were synchronized offline for the manual coding of behaviour. Each animal was coded second-by-second for five minutes per recording session, totalling 30 minutes per animal. One experimenter coded all of the videos, with a second experimenter coding a random 15% to establish reliability ( $\kappa = 0.93$ ). The following behaviours were coded using the focal sampling method: a) self-scratching, self-grooming, yawns, and body shakes (i.e. behaviours reflecting anxiety in macaques; see Coleman & Pierre (2014)); and ii) social grooming (both give and receive), which is a primary means by which macaques maintain and strengthen social relationships (Dunbar, 1998).

### **Data analysis**

To calculate attention bias to threat (ABT), the proportion of time looking at the neutral and threat stimuli (out of total time looking onscreen) was calculated separately for each neutral-threat trial, with the neutral proportion then subtracted from the threat proportion. The equivalent approach was used to calculate attention bias to LPS stimuli, i.e. positive stimuli (ABP). A linear mixed model was then utilized to investigate potential differences between rearing groups and attention bias type at the trial level, with group (mother-reared or peer-reared), condition (threat or LPS), and their interaction included as fixed effects, and subject-specific intercepts as a random effect. Social rank (randomized Elo-ratings) was also included as a covariate, and z-scored for analysis. Model residuals were checked for normality and homogeneity. Before analysis, trials where animals failed to look at the screen during facial gesture presentation or were 2.5 SDs above or below the mean were excluded. More details about rank calculation and trial exclusion can be found in the SI.

The following behavioural indices were computed based on the group observation coding: i) *anxiety frequency*, obtained by summing occurrences of self-scratching, self-grooming, yawns, and body shakes; and ii) both *duration and frequency of social engagement*, obtained by calculating total time spent in social grooming interactions and the frequency of social grooming interactions, respectively. To explore the relation between attention biases and anxiety or social engagement at the observation session level, generalized linear mixed models were run separately for average ABT and ABP per participant, with negative binomial

error distribution and a log link function. This was done with either *frequency* or *duration* of behaviour as the outcome variable. Group (mother-reared or peer-reared), ABT or ABP, and their interaction were included as fixed effects, rank (randomized Elo-ratings) as a covariate, and subject-specific intercepts as a random effect. Elo-ratings and attention biases were z-scored for analysis. R v3.6.3 (R Core Team, 2020) was utilized to conduct these analyses (see SI for package information). *P*-values for fixed effects and interactions were obtained using Type III *F* tests for linear models, and Type III Wald  $\chi^2$  tests for generalized linear models. Significant interactions between factors were followed up by planned pairwise comparisons of estimated marginal means which were Tukey-corrected for multiple comparisons. Significant interactions between factors and continuous variables (i.e. ABT or ABP) were followed up by planned comparison of the estimated marginal means of the linear trends of the continuous variable to 0 at each level of the factor. Effect sizes are reported as unstandardized model parameter estimates (in the scale of the model response variable). All animals were included in these analyses ( $n = 21$ ; 11 mother-reared, 10 peer-reared). Descriptive statistics can be found in Table 1.

**Table 1.** *Gaze measures and socioemotional behaviours.* Proportion onscreen is the proportion (M and SD) of trial time spent attending to the screen. Proportion threat, neutral, and LPS are the proportions (M and SD) of time attending to the screen spent attending to the threat, neutral, and LPS face, respectively. ABT and ABP (i.e. affective versus neutral stimuli) is the difference between proportion threat (or LPS) and neutral in the neutral-threat, and neutral-LPS trials, respectively. Anxiety and social groom frequency are the frequencies (M and SD) of anxiety-like behaviours and social grooming during the observation period. Social groom duration (M and SD) is the total amount of time (seconds) spent in grooming interactions during the observation period.

Group	Mother-reared	Peer-reared
<b>Gaze measures</b>		
Proportion onscreen	0.60 (0.15)	0.44 (0.19)
Proportion threat (neutral-threat trials)	0.455 (0.1)	0.536 (0.17)
Proportion neutral (neutral-threat trials)	0.264 (0.103)	0.145 (0.065)

Proportion LPS (neutral-LPS trials)	0.456 (0.094)	0.324 (0.1)
Proportion neutral (neutral-LPS trials)	0.225 (0.069)	0.292 (0.133)
Attention bias to threat (ABT)	0.19 (0.164)	0.386 (0.151)
Attention bias to LPS (ABP)	0.231 (0.086)	0.032 (0.14)

### **Socioemotional Behaviour**

Anxiety frequency	1.561 (0.743)	2.383 (1.114)
Social groom frequency	1.106 (0.987)	0.983 (0.713)
Social groom duration (s)	50.606 (48.466)	37.117 (31.096)

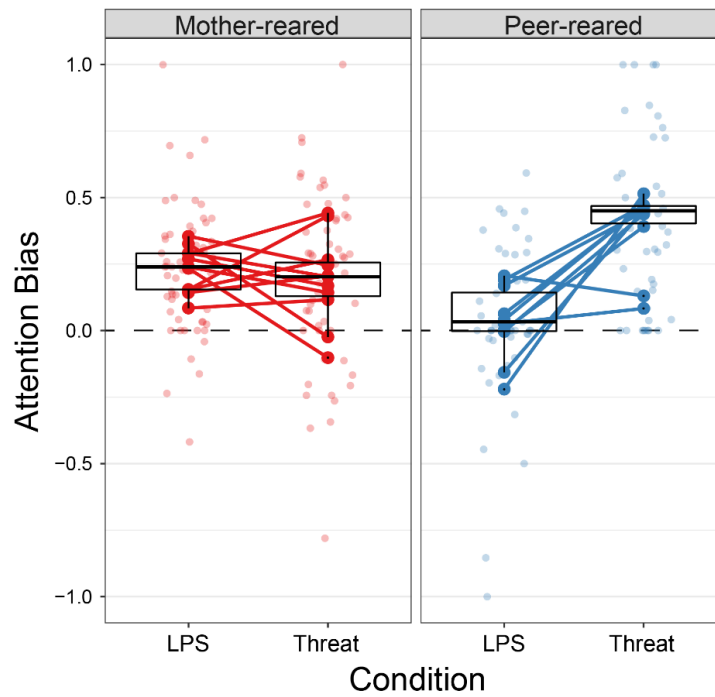
## **Results**

### **Attention bias to threat and LPS**

First we compared the attention biases to affective stimuli in the neutral-LPS and neutral-Threat conditions between the mother- and peer-reared groups. This revealed a significant main effect of group [ $F(1) = 8.288, p = 0.007$ , effect size (mother - peer) = 0.036], as well as a significant group  $\times$  condition interaction [ $F(1) = 22.101, p < 0.0001$ , mother-reared effect size (LPS – threat) = 0.036, peer-reared effect size (LPS – threat) = -0.364] (Fig. 2). Attention bias to threat (ABT) was greater in the peer-reared compared to mother-reared group [ $t(33.1) = -2.079, p = 0.045$ ], and attention bias to LPS (i.e. positive bias; ABP) was greater in the mother-reared compared peer-reared group [ $t(34.6) = 2.879, p = 0.007$ ]. In the mother-reared group, ABT and ABP were not significantly different from each other [ $t(176) = 0.628, p = 0.531$ ] but in the peer-reared group, ABT was significantly greater than ABP [ $t(178) = -5.827, p < 0.0001$ ].



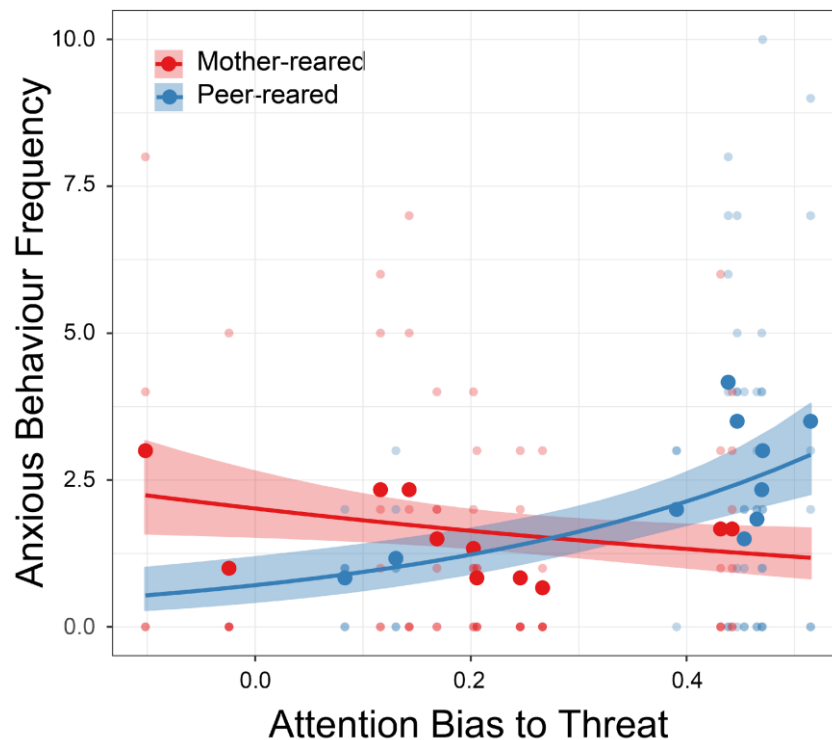
One sample *t*-tests also confirmed that in the mother-reared group, ABT [ $t(10) = 3.841$ ,  $p = 0.003$ ] and ABP [ $t(10) = 8.905$ ,  $p < 0.0001$ ] were significantly different from zero, whereas in the peer-reared group, only ABT [ $t(9) = 8.093$ ,  $p < 0.0001$ ] was significantly different from zero.



**Figure 2.** Attention biases in the neutral-LPS and neutral-threat conditions, for the mother-reared group (red; left) and peer-reared group (blue; right). Zero indicates no bias, positive values a bias towards LPS or threat versus neutral, and negative values a bias towards neutral versus LPS or threat. Light-coloured dots represent the bias in each trial, large dark-coloured dots indicate the average bias for each subject, and lines connect the average bias in the two conditions per subject. The median bias per group, first and third quartiles, and + or - 1.5 times the inter-quartile range from the first and third quartiles are also shown in the box plots.

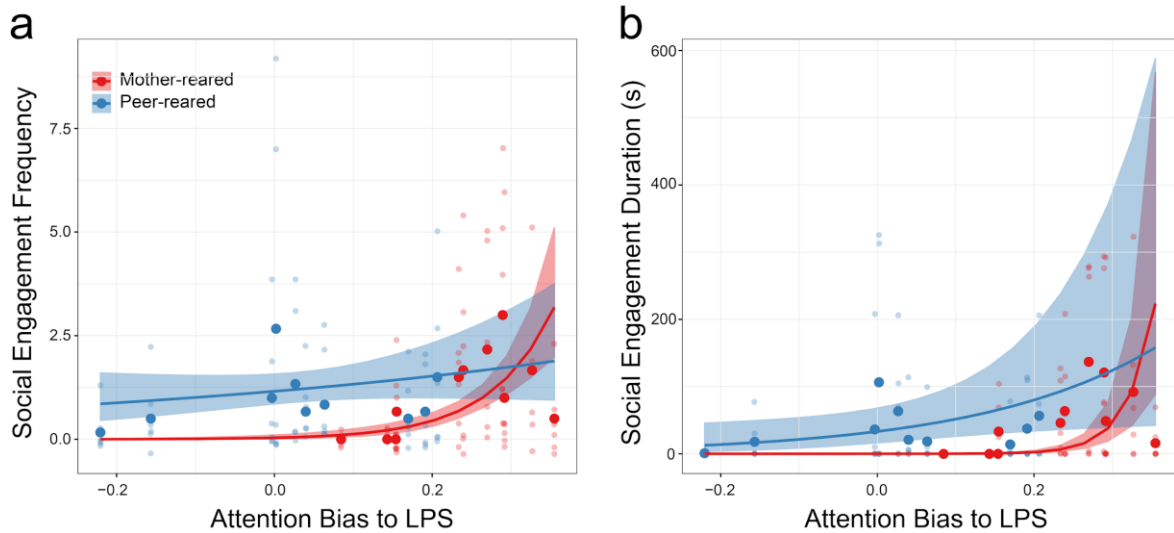
### **Relation between attention biases and socioemotional behaviour**

Having established a difference in attention biases between groups and conditions, we then sought to determine if attention biases were related to the frequency of anxious behaviour in the two rearing groups. We found a group  $\times$  ABT interaction [ $\chi^2(1) = 6.256$ ,  $p = 0.012$ , mother-reared effect size = -0.193, peer-reared effect sized = 0.506] (Fig. 3), with greater ABT related to more frequent anxiety-like behavior in the peer-reared group [ $z = 2.261$ ,  $p = 0.024$ ]. There was no significant main effect of ABP or the relation between ABP and frequency of anxious behaviour in either rearing group (both  $p > 0.458$ ).



**Figure 3.** The relation between attention bias to threat (ABT) and frequency of anxiety-like behaviour in the mother-reared (red) and peer-reared (blue) group. Each light-coloured dot represents an individual behavioural observation session, large dark-coloured dots represent the subject mean, dark lines indicate the model fit, and shaded regions around the lines denote + or - SE.

We then went on to investigate relations between attention biases and the frequency and duration of social engagement. There were significant main effects of ABP [ $\chi^2(1) = 10.064$ ,  $p = 0.002$ , effect size = 1.070], group [ $\chi^2(1) = 7.445$ ,  $p = 0.006$ , effect size (mother – peer) = -1.199], and an ABP  $\times$  group interaction [ $\chi^2(1) = 6.194$ ,  $p = 0.013$ , mother-reared effect size = 1.931, peer-reared effect size = 0.211] for social engagement frequency (Fig. 4a), with greater ABP related to more frequent social engagement in the mother-reared group [ $z = 3.172$ ,  $p = 0.002$ ]. For social engagement duration, we found significant main effects of both ABP [ $\chi^2(1) = 18.397$ ,  $p \leq 0.0001$ , effect size = 2.56] and group [ $\chi^2(1) = 12.746$ ,  $p \leq 0.001$ , effect size (mother – peer) = -60.590], and an ABP  $\times$  group interaction [ $\chi^2(1) = 9.793$ ,  $p = 0.002$ , mother-reared effect size = 4.456, peer-reared effect size = 0.665]; greater ABP was related to a longer duration of social engagement [ $z = 4.289$ ,  $p < 0.0001$  in the mother-reared group (Fig. 4b). There were no significant main effects of ABT or relations between ABT and frequency or duration of social engagement (all  $p > 0.236$ ).



**Figure.** The relations between attention bias to LPS (i.e. to positive stimuli; ABP) and social engagement in the mother-reared (red) and peer-reared (blue) group. Each light-coloured dot represents an individual behavioural observation session, large dark-coloured dots represent the subject mean, dark lines indicate the model fit, and shaded regions around the lines denote + or - SE.

## Discussion

In this study, juvenile macaques demonstrated biased attention to both threatening and affiliative dynamic facial gestures. This is in keeping with a previously demonstrated bias towards static images of open-mouth threat (Mandalaywala et al., 2014; Morin et al., 2019; Rosati et al., 2018), and provides evidence for a bias towards positive or reward-related facial gestures also. Early social deprivation was associated with the degree of bias towards both types of affective stimuli, with a greater attention bias to threat (ABT) found in peer-reared animals, and a greater attention bias to positive stimuli (ABP) found in animals reared by their mothers. Notably, ABT was also linked to anxiety-like behaviour in peer-reared animals, and ABP to levels of social engagement in mother-reared animals. These findings offer novel insights into the effects of early social adversity on affect-biased attention, and suggest that such biases could play an important role in early macaque socioemotional functioning.

The presence of a bias towards dynamic open-mouth threat in both our rearing groups provides some support for ABT emergence being part of typical macaque development. This bias was, however, greater in the peer-reared group compared to the mother-reared group. Therefore, although ABT emergence is likely normative in macaques (Mandalaywala et al., 2014; Rosati et al., 2018), it is possible that very early social deprivation can exacerbate this bias, even into the preadolescent juvenile period. Interestingly, such effects of early social

experience on ABT are similar to those seen in human children in the context of early institutionalization (Troller-Renfree et al., 2015, 2017). Mother-reared animals also showed a bias towards dynamic lip-smacking (LPS) stimuli. No previous macaque study has investigated potential effects of early adversity on an attention-bias to dynamic LPS specifically, but in line with our results, there is some evidence that early rearing status can affect infants' social responses to LPS performed by a human experimenter (Vanderwert et al., 2015). As a whole, the peer-reared group did not show significant ABP, again paralleling results from the available human literature concerning the effects of early social deprivation on ABP in pre-adolescence (Troller-Renfree et al., 2015, 2017).

Here, a greater magnitude of ABT was related to more frequent anxiety-like behaviour in the peer-reared group, suggesting that early social adversity can confer greater risk for anxiety via exaggerated or uninhibited ABT. This finding aligns with evidence suggesting that in humans, the ABT-anxiety link is not found consistently during childhood, and may be found more reliably in the context of early adverse experience. A relation between ABP and social engagement (i.e. social grooming) was also revealed in the mother-reared group, with more frequent and a longer time spent in grooming interactions associated with greater ABP. Therefore, it is possible that a bias towards reward-related stimuli also serves a positive function in macaque development. In contrast to some research with human children, we did not find a relation between greater ABP and reduced anxiety. There are a number of possible explanations for this result. For instance, some human research suggests that ABP is present in institutionalized children and linked to fewer internalizing problems only after stable fostering placement (Troller-Renfree et al., 2017). Additionally, in community samples, it may be that ABP only serves as a protective factor against anxiety in behaviourally inhibited children (White et al., 2017; Dodd et al., 2020).

In the case of atypical early parenting input, it is possible that uninhibited, exacerbated, or diminished affective attention biases are adaptive in the short-term, increasing offspring survival rates. Longer term, however, this may tie individuals to maladaptive trajectories of development (Morales et al., 2016; Pérez-Edgar et al., 2014), increasing the risk for psychopathology and social difficulties. Reduced attention to threat has already been associated with insecure and disorganized attachment in infants (Peltola et al., 2015, 2020). Parental sensitivity impacts the formation of infant-caregiver attachment (e.g. McElwain &

Booth-Laforce, 2006), with insecure and disorganized attachment implicated in the development of numerous adverse outcomes (see Ranson & Urichuk, 2008). In the case of early social deprivation, an attachment figure is completely absent. Therefore, while it may be adaptive to avoid threat in the presence of, for example, an abusive caregiver, it may be adaptive for an infant with no social buffering to be hypervigilant towards threat. This highlights an important outstanding issue, with general versus specific mechanisms linking early adversity to negative socioemotional functioning being poorly understood (McLaughlin, 2016). Clarifying these mechanisms requires consideration of how specific types of adversity may increase risk for specific adverse outcomes. In terms of a positive bias, it may be that a lack of learning opportunities to associate positive facial gestures with reward in the absence of an attachment figure influences the emergence of a positive affect bias and related social outcomes. This idea needs to be explored more explicitly in subsequent studies, but it is in keeping with evidence for atypical reward processing in the context of early social deprivation (e.g. Goff et al., 2013).

Although we found a link between ABT and anxious behaviour in juvenile macaques, it remains unclear whether ABT actually played a causal or maintaining role, or simply reflected current levels of anxiety. This remains a key unanswered question in the literature. Very little research thus far has investigated how ABT relates to or predicts anxiety longitudinally, or even the developmental trajectory of ABT itself in typical or at-risk populations. There is some evidence that ABT is unstable across childhood (Troller-Renfree et al., 2017; White et al., 2017), with ABT links to anxiety variable across this period (Nozadi et al., 2016; White et al., 2017; Dodd et al., 2020). ABP may also vary across childhood (Troller-Renfree et al., 2017; White et al., 2017). Limited research focused on how early ABP predicts subsequent anxiety and social behaviour (White et al., 2017; Dodd et al., 2020) suggests that greater ABP is linked to more positive outcomes and may serve as a protective factor against anxiety from very early childhood, but again, a lack of studies measuring both ABP and socioemotional functioning at more than one time-point limits understanding of the exact role ABP serves.

Clearly, longitudinal studies assessing both affect-biased attention and socioemotional functioning at multiple time points are now needed to better understand the role of attention biases in healthy and pathological development. Such studies will be vital to determine how increased vulnerability associated with atypical ABT might arise from a normative threat bias,

and how the presence or stability of affect-biased attention across development relates to positive and negative outcomes in different populations. As childhood and adolescence represent the core period of developmental risk for anxiety disorders (Beesdo et al., 2009), longitudinal studies across this period are of particular importance. Examining the neural learning mechanisms through which attention biases and related outcomes arise will also be critical to address these outstanding questions, and to clarify the processes underlying these relations across different points in development. Our results suggest that the macaque model is ideal for such longitudinal research, and could add considerably to our understanding on whether universal mechanisms of development underlie affect-biased attention, and whether these evolved in primates to help offspring adapt to differences in their early social environment.

In terms of neural bases, the emergence of affect-biased attention is thought to involve attentional networks supporting alerting, orienting, and executive functions, mediated by emotion processing circuitry. This includes brain structures such as the amygdala, orbital frontal cortex (OFC), regions of prefrontal cortex, and anterior cingulate cortex (Morales et al., 2016; Todd & Anderson, 2013.), but evidence from developmental populations is severely lacking. The amygdala and related circuitry may play a particularly crucial role in the processes underlying a relation between early adversity and affect-biases, with a wealth of evidence from the animal and human literature linking adversity to atypical amygdala function and development (Callaghan & Tottenham, 2016). Although the amygdala is classically described as a central node of the fear network, this region probably supports both ABT and ABP (Morales et al., 2016), with more recent studies demonstrating a large overlap of fear and reward networks (e.g. Fernando et al., 2013; Morrison & Salzman, 2010). Investigating links between development in these networks and a relation between affect-biased attention and socioemotional functioning over time will be key in future studies.

Strengths of the current study include the use of ecological dynamic stimuli and investigation of both ABT and ABP links to socioemotional behaviour. In addition, the use of a macaque model allowed for very well-controlled consideration of early environmental effects. In human research, it is often difficult to distinguish effects of the early social environment from other factors such as physical neglect, but results here provide support for the effects of very early social deprivation specifically on affect-biased attention in the pre-adolescent

period. However, there are some limitations to this study that should be noted. First, the modest sample size could represent a limitation, and it is important that the results are confirmed in larger samples. Second, these results do not speak to the issue of trait versus state anxiety, both of which have been linked to affect-biased attention (see Bar-Haim et al., 2007), which will require the measurement of anxiety-like behaviour in different contexts across an extended time scale. Third, atypical ABP may also play a role in adverse behavioural outcomes in human children (e.g. Morales et al., 2016), therefore prospective macaque research should consider this also.

There are three additional points concerning the group differences revealed here that need to be considered. Firstly, although animals in the mother-reared group remained in their natal group for the first eight months of life, they were also removed from their natal group post-weaning. Therefore, it is possible that our results were affected by ‘earlier vs later’ maternal separation. Future studies would ideally include another group of animals that were not removed from their natal social group at any point. However, our results do demonstrate clear differences between the two rearing groups, and are in keeping with previous findings concerning development of affect biased attention in individuals who have been exposed to early psychosocial adversity versus not (e.g. Troller-Renfree et al., 2015, 2017). Behaviour in our peer-reared group (e.g. increased anxiety-like behaviour) does suggest that their risk for long-term poor outcomes is greater than in the mother-reared group, perhaps highlighting the first months of life as a sensitive period for the impact of social adversity on certain aspects of socioemotional development. Secondly, peer-reared animals often obtain a lower social rank than mother-reared animals (e.g. Dettmer et al., 2016), and hypothetically, exposure to more threat in the environment as a result of low rank may have a direct effect on anxiety, or indirectly via effects on attention biases. In our sample, peer-reared animals did tend to be lower-ranking (see SI), though the inclusion of rank as a covariate in our models did not change relations between early adversity, gaze biases, and socioemotional behaviour. This suggests that early social adversity affects rank and gaze bias/behaviour independently, but it is still possible that rank moderates the mediating effects of attention biases. Indeed, some previous work with adult macaques has found that social dominance can influence attention towards social stimuli (e.g. Schülke et al., 2020). This possibility is an interesting avenue for future longitudinal work with larger samples, especially in the case of natural variation in early social

experience. And thirdly, while social grooming is often used as a measure of prosocial engagement in macaques, grooming is a complex behaviour with context-dependent effects of hormonal and neural responses in NHPs (e.g. Shutt et al., 2007; Crockford et al., 2013). Elucidating these context-dependent effects such as the relative rank of the actor and receiver, and their relationship to affect-biased attention is an important avenue for future research.

To conclude, this study demonstrates that juvenile, pre-adolescent macaques are biased towards looking at both threatening and affiliative dynamic facial gestures, but that the degree of attention bias is influenced by early social deprivation. Furthermore, links between ABT and anxiety in the context of early adversity, and an absence of ABP links with social engagement, suggests that affect-biased attention could play an important role in rhesus macaque development. Longitudinal research concerning the mechanisms underlying these relations is now required to determine the factors conferring greatest risk for anxiety, as well as those implicated in positive social outcomes and resilience.



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### **Author Contributions**

HR and PFF designed the study; HR, AM, and MB collected the data; HR analysed the data; HR and PFF wrote the manuscript; HR, AM, MB, SBH, and PFF all reviewed the manuscript.

### **Conflict of Interest Statement**

The authors have no conflict of interest to declare.



## ***Supplementary information***

### **Methods**

#### ***Subjects***

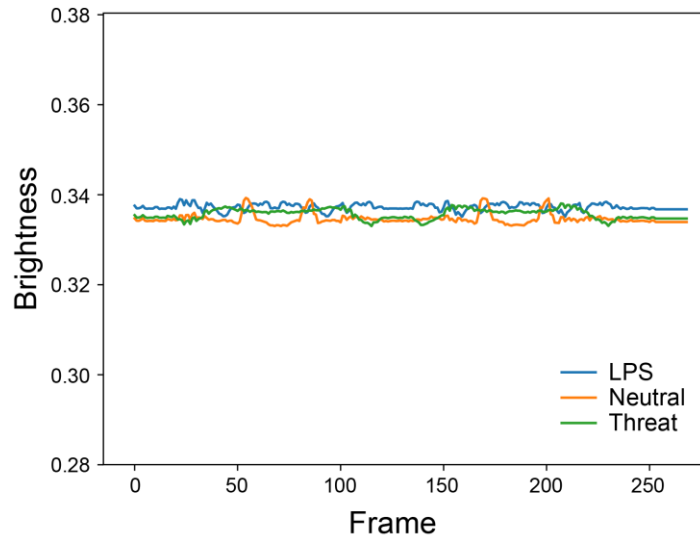
Peer-reared animals were raised from birth in a nursery with access to same-aged peers; this peer-rearing protocol was based on that of Shannon et al. (1998). At eight months postpartum, mother-reared and peer-reared subjects were placed into a single social group. Animals were relocated to their current location at two years of age and are housed together. Animals live in semi free-ranging conditions, with access to both indoor and outdoor areas. As part of a wider longitudinal study, animals are temporarily relocated once a year to a nearby location in groups of 5-6 animals. All groups contain a balanced mix of mother-reared and peer-reared animals, with groups housed in an indoor enclosure. This enclosure is enriched to allow for meaningful activities and expression of the animals' full behavioural repertoire. Assessments for the current study were conducted a minimum of 10 days after this relocation.

#### ***Facial gesture stimuli***

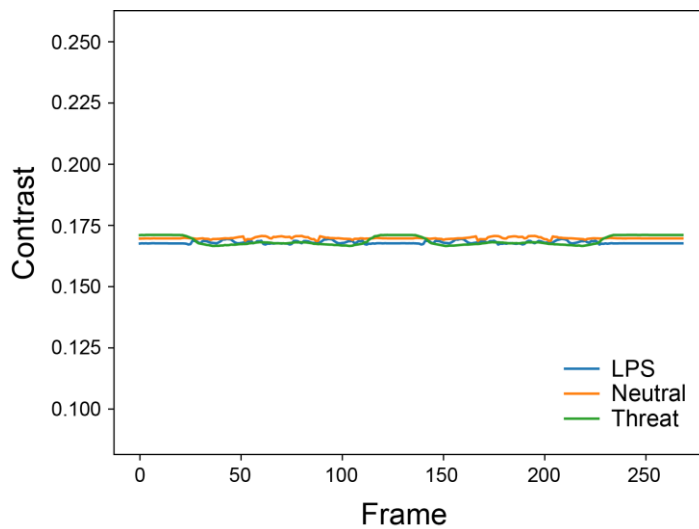
To calculate brightness, contrast, spatial frequency, and overall movement, video frames were first converted to greyscale by averaging over the RGB colour dimension. Brightness was computed as the normalized average of all pixel values, and contrast as the standard deviation. Spatial frequency was computed using a two-dimensional Fourier transform, which was then averaged over the azimuth to create a one-dimensional vector of power at each spatial frequency. Motion was computed using the Farneback method (Farneback, 2003) for optical flow, using a classical pyramid image scale with 3 levels, an averaging window size of 15 pixels, 3 iterations per pyramid, a pixel neighborhood size of 5, and a Gaussian with SD equal to 1.2 for derivative smoothing; movement was then converted to pixels per second.

The values averaged over all frames from each video for each facial gesture type were as follows: a) Lip-smacking (LPS), brightness = 0.337, contrast = 0.168, motion = 52.13 pixels per second; b) Neutral, brightness = 0.335,

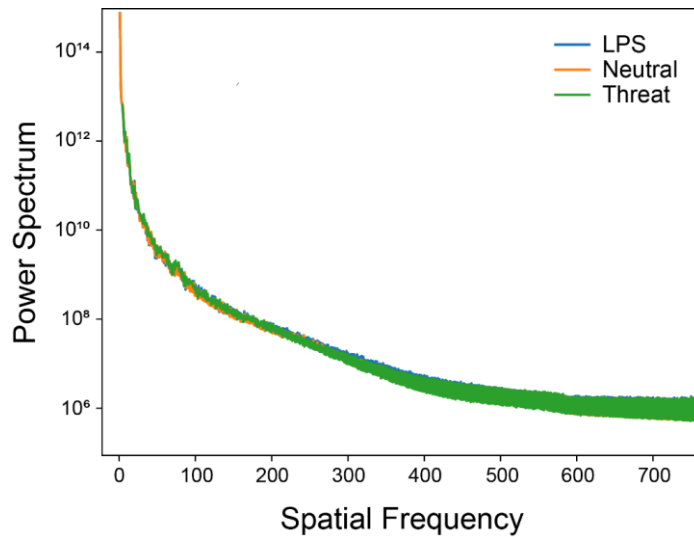
contrast = 0.2, motion = 41.86 pixels per second; and c) Threat, brightness = 0.34, contrast = 0.2, motion = 42.81 pixels per second. Brightness, contrast, spatial frequency, and motion are illustrated in Figures S1-S4.



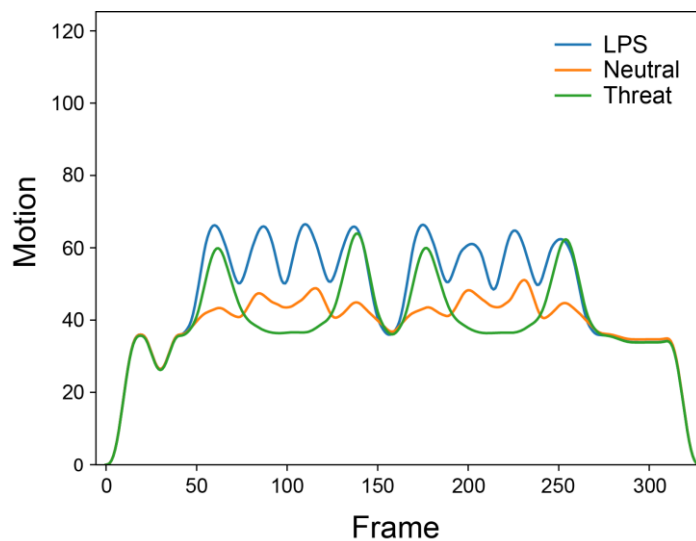
**Figure S1.** Brightness for LPS (blue), neutral (orange), and threat (green) videos computed as the normalized average of all pixel values.



**Figure S2.** Contrast for LPS (blue), neutral (orange), and threat (green) videos computed as the standard deviation of all pixel values.



**Figure S3.** Spatial power spectrum for LPS (blue), neutral (orange), and threat (green) videos computed using a two-dimensional Fourier transform, averaged over the azimuth to create a one-dimensional vector of power at each spatial frequency.



**Figure S4.** Motion (pixels per second) for LPS (blue), neutral (orange), and threat (green) videos computed using the Farneback method for optical flow.

### Data analysis

R v3.6.3 (R Core Team, 2020) and the lme4 v1.1.21 (Bates et al., 2015), nlme v3.1.144 (Pinheiro et al., 2020), lsmeans v2.30.0 (Lenth, 2016), the glmmADMB v0.8.3.3 (Fournier et al., 2012; Skaug et al., 2016), and car v3.0.6 (Fox & Weisberg, 2019) packages were utilized to conduct these analyses.

## **Results**

### ***Gaze bias task: Trial exclusion in the different conditions***

A generalized linear model with a Poisson distribution and logit link function was run to confirm that the number of gaze bias trials did not differ between groups or conditions after trial rejection. This revealed no effect of group, condition, or their interaction on the number of trials. Mean trials (out of the 5 ABT trials and 5 ABP trials per subject) included for mother-reared animals were as follows: ABT,  $M = 4.818$ ,  $SD = 0.405$ , range 4-5; ABP,  $M = 4.909$ ,  $SD = 0.302$ , range 4-5. Mean trials included for peer-reared animals were as follows: ABT,  $M = 4.7$ ,  $SD = 0.483$ , range 4-5; ABP,  $M = 4.6$ ,  $SD = 0.699$ , range 3-5.

### ***Social rank calculation***

Rank of individual animals was established via Elo-ratings (Sanchez-Tojar et al., 2018; R packages 'EloRating' v 0.46.11; Neumann & Kulik, 2020; 'aniDom' v0.1.5; Farine & Sanchez-Tojar, 2021), with winners and losers of agonistic interactions, classified as aggressive or submissive, identified from 60 minutes of behavioural observation per animal (four observations per week (two mornings, two afternoons) for three weeks). Coded behaviours included displacement, threat gestures, aggression, fear grimace, and present genitals (Dettmer et al., 2016; Wooddall et al., 2017). There were a total of 198 interactions,  $M=9.41$  and  $SD=1.81$  per group. As the hierarchies were highly stable over the course of the observation period ( $S$  index: 0.95 – 0.99;  $M=0.97$ ;  $SD=0.02$ ), we used randomized Elo-ratings (over 100 temporally shuffled randomizations). Animals in the peer-reared ( $M=-201.25$ ,  $SD=180.21$ ) group attained a lower rank on average than the mother-reared ( $M=182.96$ ,  $SD=141.87$ ) group [ $t(17.11)=5.39$ ,  $p < 0.001$ ].

### ***Influence of sex***

To control for a potential influence of sex on our results, we also ran all analyses reported in the main text with sex included as a covariate. All animals were included in these analyses; 11 mother-reared (six female) and 10 peer-reared (five female). The pattern of results revealed were identical to those

reported in the main manuscript, suggesting that differences between groups remain even when accounting for sex.

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## Deprivation, structural brain connectivity, and anxiety

Psychosocial deprivation in the form of institutional rearing is associated with poor outcomes spanning multiple developmental domains, including increased risk for various psychological and social difficulties. These include psychiatric disorders associated with emotion dysregulation, such as anxiety, depression, and externalizing problems (e.g. Bos et al., 2011; Humphreys et al., 2015). Previous research suggests that alterations in brain development linked to early social experience play a crucial role in the increased emotional dysregulation often seen in institutionalized children (e.g. Tottenham et al., 2010; Troller-Renfree et al. 2015). However, many questions remain about the specific neurocognitive mechanisms that contribute to this dysregulation and subsequent risk for poor outcomes, especially across key developmental transition periods when these disorders are most likely to emerge, such as adolescence (Kessler et al., 2005).

Accordingly, we made longitudinal observations of our peer-reared and mother-reared animals to track anxiety-like behavior from late childhood into early adulthood (i.e. 2.5, 3.5, and 5 years). At the same time-points, we acquired anatomical and diffusion MRI, enabling us to use DTI to investigate how development in structural neurocircuitry linked to emotion regulation and anxiety may be impacted by early psychosocial deprivation in macaques, and how this relates to actual anxiety-like behaviour. Note, early psychosocial adversity has previously been linked to problems with emotion processing, regulation, and anxiety in macaques (e.g. Dettmer et al. 2012; Rayson et al., 2021). More specifically, we hypothesized that peer-reared animals would demonstrate greater anxiety across time, and that this would be linked to increased emotional reactivity. We also predicted that white matter microstructure in fronto-limbic and fronto-striatal tracts would modulate these relationships. Fronto-limbic and fronto-striatal structural connectivity has been associated with early institutionalization in some research (e.g. Bick et al., 2015), and limbic and striatal connectivity with prefrontal cortical regions is associated with anxiety disorders (Kenwood et al., 2022).

The particular white matter ROIs/tracts of interest for our analyses included the uncinate fasciculus (UF), the superior cingulum (SC), the hippocampal cingulum (HC), the fornix (FX), the anterior limb of the internal capsule (ALIC), the anterior corona radiata (ACR), and the external capsule (EC). These fronto-limbic and fronto-striatal tracts have all been linked to early psychosocial deprivation and to anxiety in humans, though little research



linking this to poor outcomes have been conducted, particularly in terms of longitudinal development across core periods of risk (e.g. adolescence) or in macaques.

Note for all analyses presented here, R v3.6.3 (R Core Team, 2020) was utilized. *P*-values for fixed effects were obtained using Type III Wald  $\chi^2$  tests. Significant interactions between factors were followed up by planned pairwise comparisons of estimated marginal means which were Tukey-corrected for multiple comparisons. Significant interactions between factors and continuous variables were followed up by planned comparison of the estimated marginal means of the linear trends of the continuous variable to 0 at each level of the factor. Residuals for each model were inspected for outliers using Cook's distance, but none required removal.

Presented below is a summary of our preliminary findings thus far.

## ***Peer-rearing is associated with increased anxiety compared to mother-rearing***

### **Methods**

At each time-point (2.5, 3.5, and 5 years), video recordings of the social group (50fps) were made two times per week, once in the morning and once in the afternoon, for three weeks. Two cameras were used to capture the whole home enclosure and were synchronized offline for the manual coding of behaviour. Each animal was coded second-by-second for ten minutes per recording session, totalling 60 minutes per animal, per time-point. One experimenter coded all the videos, with a second experimenter coding a random 10% at each time-point to establish reliability (all  $\kappa > 0.85$ ). The following behaviours were coded using the focal sampling method for the anxiety measure: a) self-scratching, self-grooming, yawns, and body shakes (i.e. behaviours reflecting anxiety in macaques; see Coleman & Pierre (2014)). For analysis, a negative binomial generalized mixed model was run with group (mother-reared/peer-reared) and time-point (2.5/3.5/5 years) as fixed effects, and subject-specific intercepts as a random effect. Frequency of anxiety-like behaviour was used as the outcome measure, and sex was also controlled for in the model.

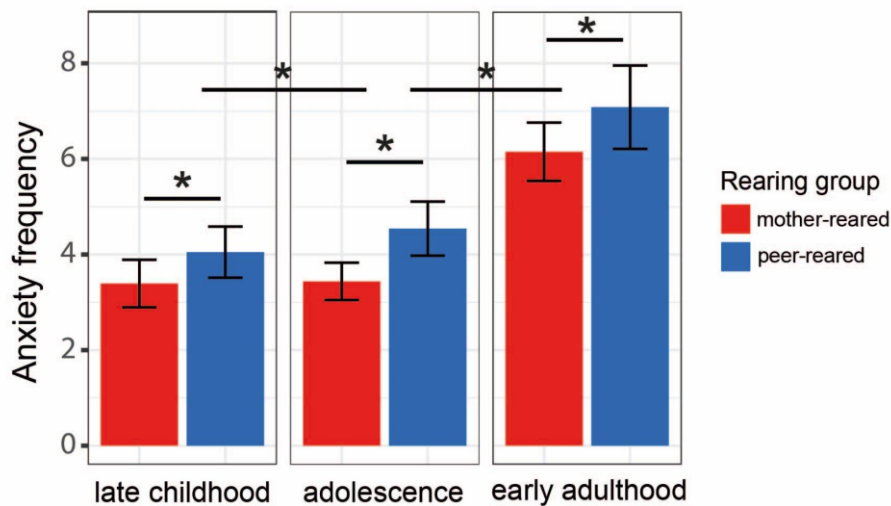
### **Results**

Results revealed a main effect of group [ $\chi^2(1) = 4.46, p = 0.035$ ], with greater anxiety in peer-reared animals across time. A main effect of time-point was also found [ $\chi^2(1) = 17.7, p$

< 0.001], with anxiety increasing in all animals over time. These findings are illustrated in Fig. 1.

## **Conclusion**

In accordance with our hypothesis, early psychosocial deprivation is linked to increased risk for anxiety across adolescence into early adulthood in rhesus macaques.



**Figure 1.** Frequency of anxiety-like behaviour at each assessment time-point. Across time, greater anxiety was found in the peer-reared (blue) versus mother-reared (red) group, with anxiety increasing in both groups with age. Significant effects are denoted by \*, and error bars represent +/- SE.

## ***Peer-rearing is associated with greater emotional reactivity which is linked to anxiety***

### **Methods**

At all time-points, a version of the human intruder paradigm (Kalin & Shelton, 1989) was used to assess subjects' reactivity to potential social threat; an unfamiliar human intruder. This task is often used as an indicator of emotional and behavioural regulation problems in macaques. Each subject was temporarily separated from their social group and placed into the testing area in another section of the room; an 87 × 100 × 120cm enclosure with a clear panelled front. Animals were given five minutes to habituate to the enclosure once separated. Note, all animals had already been well familiarized with this process of separation into the testing enclosure before the day of assessment. Animals were recorded during the task using two cameras (50fps), which were then synchronized offline. The task comprised four conditions: i) 'alone 1', no intruder present; ii) 'profile', intruder stood with their head turned away from the subject to avoid eye contact (low threat); iii) 'alone 2', no intruder present; and

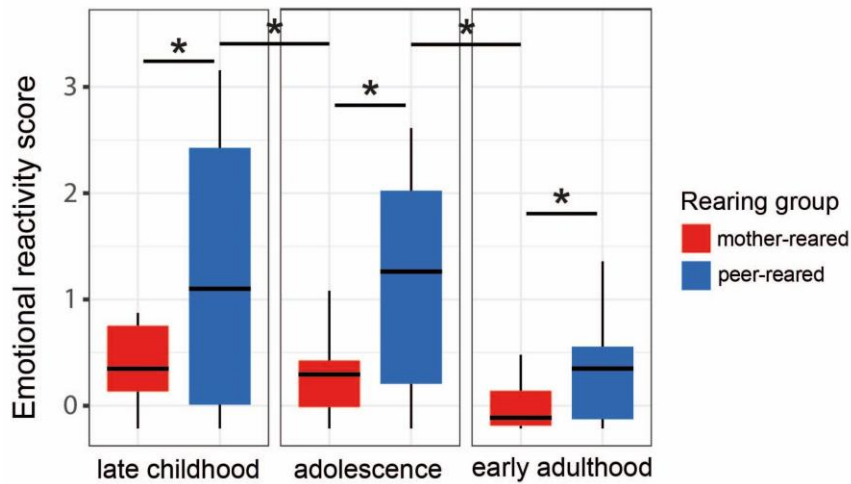
iv) 'stare', intruder stood with their head facing forward and making eye contact with the subject (high threat). In the profile and stare conditions, the intruder stood 1m from the front of the testing enclosure. Each condition lasted 2 minutes. As some coded behaviours had a duration and some did not, a combined z-score measure of reactivity was calculated based on all responses directed towards the intruder (i.e. threatening, fearful, and affiliative gestures) in the high threat condition (stare), which was used as the outcome variable for analysis. A linear mixed model was run with group (mother-reared/peer-reared) and time-point (2.5/3.5/5 years) as fixed effects, and subject-specific intercepts as a random effect. A negative binomial generalized mixed model was then run to examine the relationship between reactivity and anxiety-like behaviour in the everyday social environment (see section a) above). Reactivity and time-point (2.5/3.5/5 years) were included as fixed effects, and subject-specific intercepts as a random effect. Frequency of anxiety-like behavior was used as the outcome measure, and sex was controlled for.

## **Results**

Results for the analysis predicting reactivity revealed a main effect of group [ $\chi^2(1) = 4.52, p = 0.033$ ], with greater reactivity in the nursery-reared group compared to the mother-reared across time. A main effect of time was also revealed [ $\chi^2(1) = 10.39, p = 0.006$ ], with reactivity decreasing across time overall. Note, no differences between groups were found in other types of defensive responses or behaviours during this task (e.g. freezing). These findings are illustrated in Fig. 2. The analysis predicting anxiety revealed a main effect of reactivity [ $\chi^2(1) = 6.77, p = 0.009$ ], with greater reactivity associated with more anxiety. A main effect of time was also found, with anxiety increasing with age [ $\chi^2(1) = 30.56, p < 0.001$ ].

## **Conclusion**

Although reactivity decreases between pre-adolescence and early adulthood overall, reactivity remains greater in the peer group compared to the mother group over time. Higher reactivity also predicted more frequent anxiety, suggesting that emotion dysregulation in macaques is linked to increased anxiety risk.



**Figure 2.** Emotional reactivity at each assessment time-point. Across time, greater reactivity in the stare (high threat) condition was found in the peer-reared (blue) versus mother-reared (red) group, though reactivity decreased with age overall. Significant effects are denoted by \*, and error bars represent +/- SE.

## ***Rearing condition associated with differences in FA in limbic white matter tracts***

### **Methods**

For each ROI, methods described in Chapter 4 were used to calculate the mean values of fractional anisotropy (FA), which represents the degree of directionality of random water diffusion. Higher FA is often interpreted to reflect greater white matter integrity. Linear mixed models were run for each DTI ROI and hemisphere, with group (mother-reared/peer-reared) and time-point (2.5/3.5/5 years) as fixed effects, and subject-specific intercepts as a random effect. FA was the outcome variable, and sex was controlled for in all models.

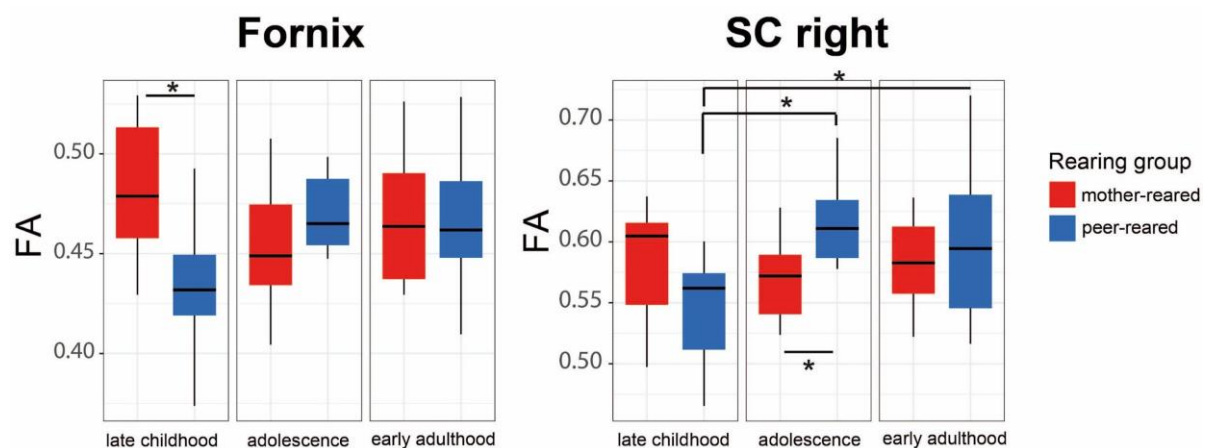
### **Results**

For the right SC, a group by year interaction was revealed [ $\chi^2(2) = 8.95, p = 0.01$ ]; at the second time-point, FA in the peer-reared group was higher ( $p = 0.03$ ), and FA was greater at time-points two and three compared to one in the peer group (both  $p < 0.05$ ). Comparable results were found for the left SC. For HC, a group by year interaction was revealed [ $\chi^2(2) = 9.62, p = 0.008$ ]; FA was greater at time-points two and three compared to one in the mother-reared group (both  $p < 0.001$ ). For the left HC, only a main effect of age was revealed [ $\chi^2(2) = 9.51, p = 0.009$ ]. For the fornix, a group by year interaction was revealed [ $\chi^2(2) = 9.67, p = 0.008$ ]; FA was greater in the mother-reared group at the first time-point ( $p = 0.004$ ). A main effect of year was found for left ALIC [ $\chi^2(2) = 9.7, p = 0.008$ ], with FA increasing over time. For

right ACR, there was a main effect of year [ $\chi^2(2) = 14.56, p < 0.001$ ], with FA increasing over time. Finally, for right EC, a main effect of year was also found [ $\chi^2(2) = 6.4, p = 0.04$ ], with FA increasing over time. No effects were found for the UF.

## **Conclusion**

While white matter integrity tended to increase with age, with changes in the superior cingulum and fornix influenced by rearing condition. The superior cingulum (SC) integrates many cortical structures such as the anterior cingulate, ventromedial prefrontal, orbitofrontal and parietal cortices, as well as cortico-subcortical regions (e.g. amygdala/thalamus-PFC), and is associated with emotion, reward, and motor processes (Bubb et al., 2018). The fornix connects the hippocampus to subcortical areas including the hypothalamus, and to cortical areas such as prefrontal and cingulate regions; related to memory and spatial association (Catani et al., 2013). Both tracts are important parts of the limbic system and play an important role in emotion regulation.



**Figure 3.** FA at each assessment time-point. FA in the fornix in the two rearing-groups (left) and FA in the right superior cingulum (SC) in the two rearing-groups (right). Significant effects are denoted by \*, and error bars represent +/- SE.

## ***Structural connectivity differentially related differentially to anxiety in the two rearing groups***

### **Methods**

At each time-point (2.5, 3.5, and 5 years) high resolution anatomical (T1/T2) and diffusion MRI scans were acquired (see Chapter 4 for detailed methods). For analysis, separate negative binomial generalized mixed models were run for each ROI (UF, SC, HC, FX, ALIC, ACR,

and EC) and hemisphere (right and left) with group (mother-reared/peer-reared), time-point (2.5/3.5/5 years), and FA included as fixed effects, and subject-specific intercepts as a random effect. Frequency of anxiety-like behavior was used as the outcome measure for analysis, and sex was also controlled for in all models. As a number of analyses were run predicting the same outcome (13 in total), our  $p$ -value for significance was set at 0.004 after Bonferroni correction.

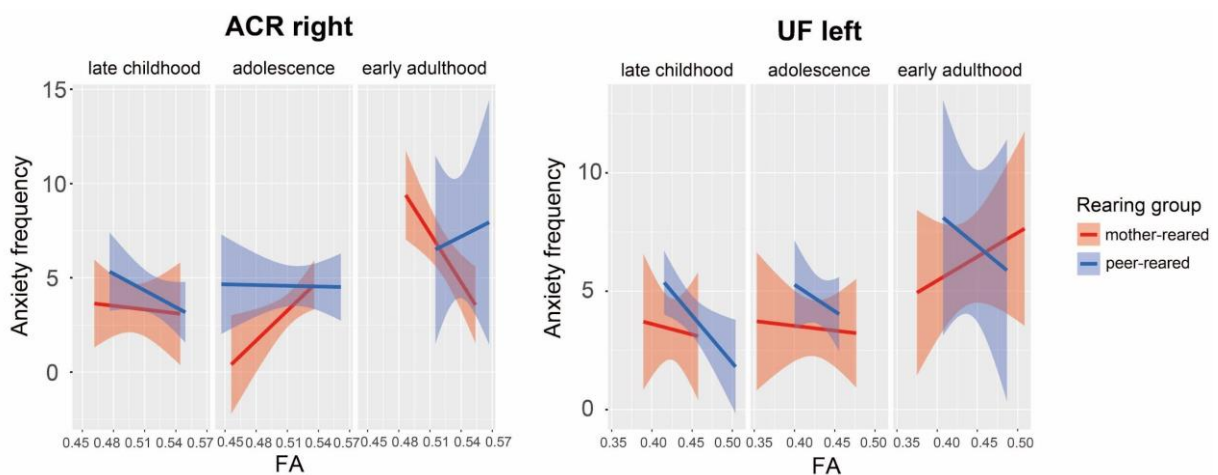
## **Results**

Results for the UF and ACR tracts are presented here. For the right UF, a significant main effect of FA was revealed [ $\chi^2(1) = 30.83, p < 0.001$ ], with greater FA predicting less anxiety across time. For the left UF, a significant interaction was found between group and FA was found [ $\chi^2(1) = 16.60, p < 0.001$ ], with a negative FA anxiety relationship stronger in the peer-reared compared to mother-reared group ( $p < 0.001$ ), and a significant interaction between year and FA [ $\chi^2(2) = 21.77, p < 0.001$ ], with a negative FA-anxiety relationship disappearing by the third time-point (both  $p < 0.006$ ). For the right ACR, a significant group by year by FA interaction was revealed [ $\chi^2(2) = 204.63, p < 0.001$ ], with a negative FA-anxiety relationship at time points one and three but a positive FA-anxiety relationship at time-point two for the mother-reared group (all  $p < 0.001$ ), and a negative relationship only at the first two time-points for the peer-reared group (both  $p = 0.003$ ). The two rearing groups were different from one another at the last two time-points (both  $p < 0.001$ ). For the left ACR, a significant year by FA interaction was found [ $\chi^2(2) = 280.8, p < 0.001$ ] with higher FA linked to less anxiety at time-points one and two ( $p < 0.001$ ).

## **Conclusion**

Early psychosocial deprivation has long-term effects on emotion regulation and anxiety in macaques. Development of structural connectivity in fronto-limbic and fronto-striatal brain circuitry appears to modulate this relationship with anxiety, with group differences found in the relationship between white matter integrity and anxiety in the uncinate fasciculus (UF; a tract that connects the amygdala and prefrontal cortex) and the anterior corona radiata (ACR; a tract containing thalamic and striatal projections from the internal capsule to the prefrontal cortex). Results for the left UF could suggest that while a relationship between higher FA remains for the peer-reared group across time, in general, this relationship weakens with age. This weakening relationship across adolescence is in keeping with findings in the

human literature (Hein et al., 2018), with the continuance of this relationship in the peer-reared group perhaps indicating a form of resilience or protection in the context of early psychosocial adversity. Alternatively, this could reflect atypical development in the peer-reared group, with normative changes not taking place, being delayed, or resulting from the premature closing of the related developmental plasticity window. In either case, although this may be adaptive in early life, it may also increase risk for atypical brain development and related anxiety later on. For ACR, results in the mother-reared group suggest some reorganization takes place in fronto-striatal circuitry that relates to anxiety in adolescence. This may not, however, take place in the peer-reared group, which could suggest a long-lasting or sleeper effect of early psychosocial deprivation on fronto-striatal connectivity. One interesting idea is that the maintenance of the fronto-amygdala relationship with anxiety and a lack of a relationship with fronto-striatal connectivity in adulthood in peer-reared animals is related to compensatory mechanisms of development early on in life, whereby certain aspects of threat processing and executive function are prioritized over others, but that lead to atypical brain development and increased risk for poor outcomes across subsequent developmental periods. Such ideas involving compensatory mechanisms are explored more in Chapters 4 and 5 of this thesis.



**Figure 4.** Relationships between FA, rearing group, and anxiety in white matter ROIs. Greater integrity in uncinate fasciculus (UF; left) predicted less anxiety at the first two time-points, but a stronger relationship in peer-reared animals across all time-points. Greater integrity in the anterior corona radiata (ACR; right) in mother-reared group predicted less anxiety in childhood and early adulthood, but more anxiety in adolescence; while in peer-reared group greater integrity in the right ACR predicted less anxiety in childhood and adolescence, but not in early adulthood. Error bars represent  $\pm$  SE.

Next steps in the analysis of this data include the following: i) finish analyses concerning how DTI ROIs and rearing group predict anxiety, including examination of other DTI metrics (RD, AD, MD); ii) consider how emotional reactivity rather than group interacts with white matter integrity to predict anxiety; iii) consider other structural measures of brain development, such as regional volumes and cortical thickness; iv) use of analyses to better examine trajectories of change (e.g. prospective analyses, hierarchical growth curve models); v) and exploration of how both emotion dysregulation and executive function may interact to predict poor outcomes such as anxiety.



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## **APPENDIX B.**

### **Structural brain development between late childhood and adulthood**

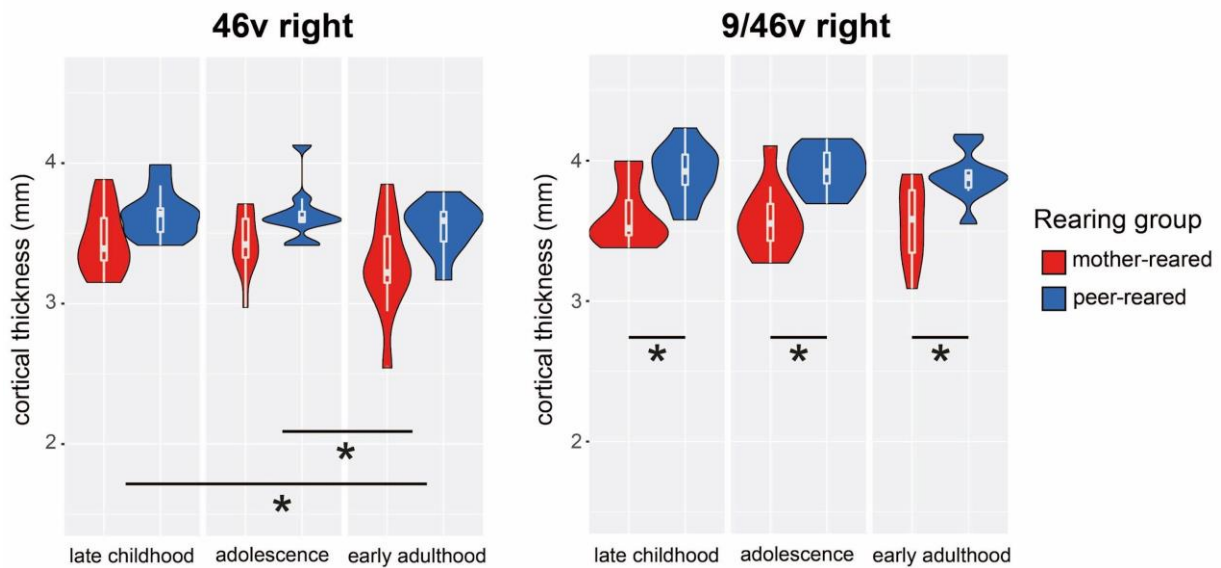
In this appendix, results are presented from analyses conducted to investigate thickness in prefrontal cortex (PFC) ROIs and fractional anisotropy in the superior longitudinal fasciculus (SLF; fronto-parietal white matter tract) across all three project time-points (early childhood, adolescence, and early adulthood). In chapter 4, analyses included the last two time-points only (adolescence and early adulthood).

Analyses including all three-project time-points for the fronto-striatal tracts looked at in Chapter 4 can also be found in Appendix A.

## **Effects of early psychosocial deprivation on PFC thickness**

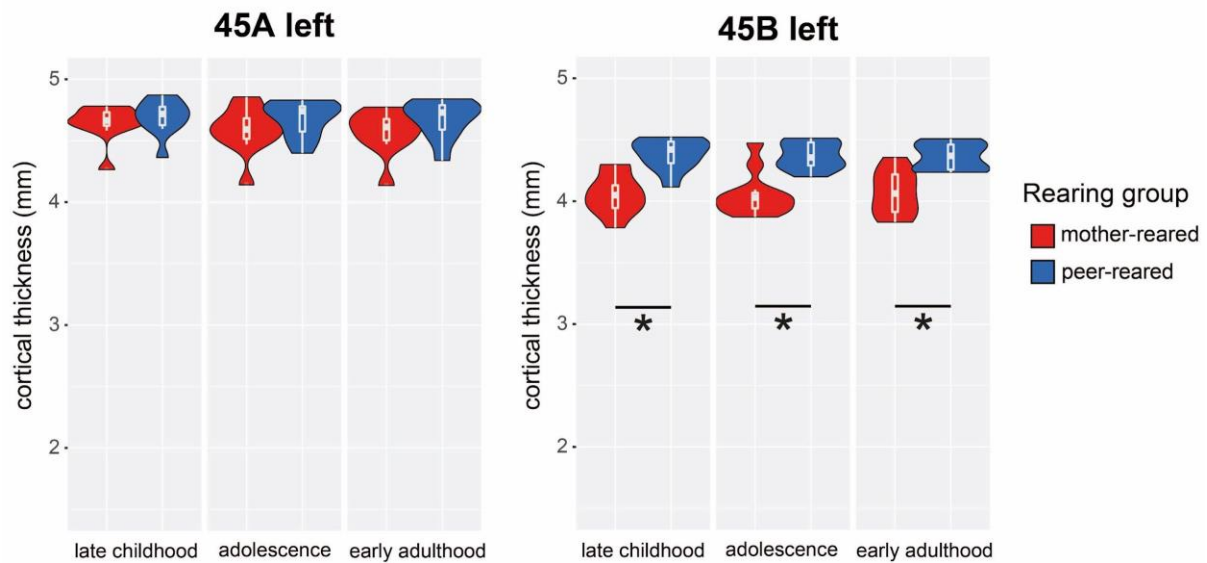
We investigated the effects of early psychosocial deprivation on the development of two lateral prefrontal regions implicated in EF (dlPFC and vlPFC) from late childhood into early adulthood. We used a mixed-model approach for analysis, with group (mother-reared/peer-reared), time-point (2.5/3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. For each area, analyses for the right and left hemispheres were run separately. Sex was controlled for in all analyses.

For dlPFC, a significant main effect of time-point was found in several areas in the left 46d area [ $\chi^2(2) = 6.912, p = 0.031$ ], and in the right and left 46v areas [right,  $\chi^2(2) = 14.410, p < 0.001$ ; left,  $\chi^2(2) = 6.333, p = 0.042$ ], with a trend also found in the right 9/46v area [ $\chi^2(2) = 5.9, p = 0.052$ ] (Figure 1). However, only in the right 46v area the follow-ups were significant, with both rearing groups showing a decrease in cortical thickness over time; thickness in late childhood and adolescence was greater than in early adulthood (both  $p < 0.006$ ). Additionally, a significant main effect of group was revealed in the right 9/46v area [ $\chi^2(1) = 4.193, p = 0.041$ ], with greater thickness in the peer-reared group compared to the mother-reared group.



**Figure 1.** Group differences in cortical thickness in right 46v and 9/46v areas of dlPFC. A decrease in thickness in the right 46v area was found in both groups from adolescence into early adulthood. Across all time-points, greater cortical thickness was found in the peer-reared (blue) versus mother-reared (red) group in the right 9/46v area. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting +/- SE and \* denoting significant differences.

For vlPFC, a significant main effect of group was found in two areas (Figure 2). Across time, the peer-reared group had greater cortical thickness compared to the mother-reared group in the left 44 area [ $\chi^2(1) = 7.815, p = 0.005$ ], and in the right and left 45B areas [right,  $\chi^2(1) = 14.410, p < 0.001$ ; left,  $\chi^2(1) = 17.995, p < 0.001$ ]. In addition, in the left 45A area, we found a main effect of time-point [ $\chi^2(2) = 7.728, p = 0.021$ ], however the follow-ups were not significant. See Chapter 5 of this thesis for discussion of these results.

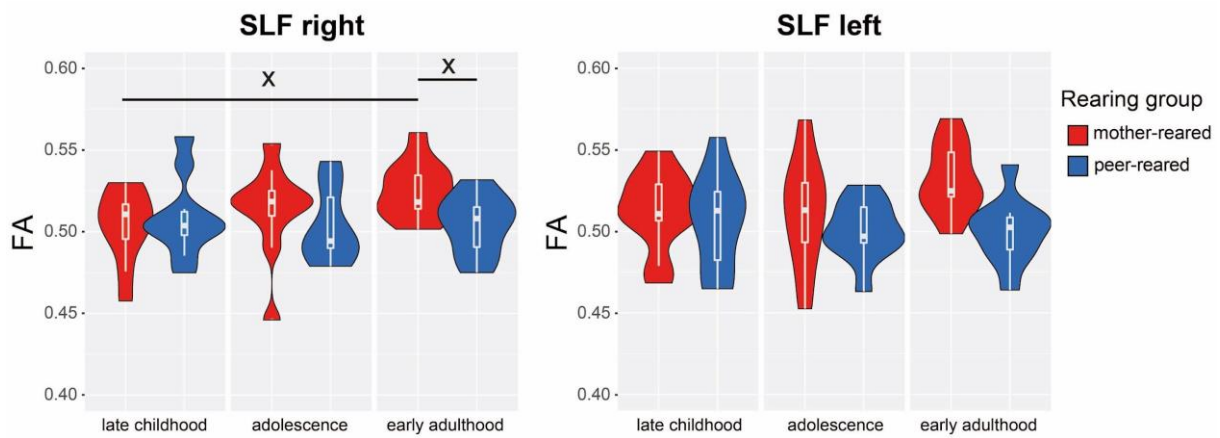


**Figure 2.** Group differences in cortical thickness in the left 45A and the left 45B areas of vIPFC. Thickness in the left 45A across time in both groups. Across time, greater cortical thickness was found in the peer-reared (blue) versus mother-reared (red) group in the left 45B area. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting +/- SE and \* denoting significant differences.

## Effects of early psychosocial deprivation on white matter integrity in SLF

We also investigated the effects of early psychosocial deprivation on the development of SLF from childhood into early adulthood. We again used a mixed-model approach for analysis, with group (mother-reared/peer-reared), time-point (2.5/3.5/5 years), and their interactions included as fixed effects, and subject-specific random intercepts. Sex was controlled for in all analyses.

In the right SLF we found an effect of time-point [ $\chi^2(2) = 8.646, p = 0.013$ ], however, the follow-ups were not significant (Figure 3). Also in the right SLF, there was a trend for the group by time-point interaction [ $\chi^2(2) = 5.863, p = 0.053$ ], with integrity in the mother-reared group in early adulthood differing from late childhood [ $t(1) = -2.938, p = 0.015$ ], and with a trend for greater integrity in early adulthood in the mother-reared versus peer-reared group [ $t(1) = 1.980, p = 0.054$ ]. In the left SLF, a main effect of time-point was found [ $\chi^2(2) = 7.386, p = 0.025$ ], but the follow-ups were not significant. See Chapter 5 for discussion of these results.



**Figure 3.** Group differences in FA in the superior longitudinal fasciculus (SLF). In the right SLF, a trend was found suggesting that integrity of SLF was greater in the mother-reared (red) versus peer-reared (blue) group in early adulthood, with integrity in mother-reared group differing from late childhood to early adulthood. In the left SLF, integrity in both groups across time is shown. Violin plots represent the density of the variable, while box-plot represent summary statistics, with error bars reflecting  $\pm$  SE and x denoting trends.

## **APPENDIX C.**

### **Poster presentations**



# Poster and short talk presented at NeuroFrance (2021) and at the Budapest CEU conference on Cognitive Development (2021)

The work on which this poster is based has now been published (Massera et al, *in press*). The manuscript is presented in Chapter 3 of this thesis.

## Early social adversity influences executive function in juvenile macaques

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<h3>1. Introduction</h3> <p>Executive function (EF) is an umbrella term for a group of domain general, interrelated cognitive skills that underlie the organization and control of goal-directed behaviour.</p> <p>EF deficits associated with neurodevelopmental disorders (e.g. ADHD, ASD, internalizing and externalizing disorders) [1,2]</p> <p>Early social deprivation has been linked to EF deficits [3,4]</p> <p>But, what are the effects of early social deprivation on EF across different periods of development?</p>	<h3>3. Behavioural assessment</h3> <h4>A not B task</h4> <p>One experimenter stood in front of the monkey and hid a piece of food in one position (A trials), and then changed the hiding position (B trials) after the subject had the opportunity to retrieve the food from the first hiding place a number of times [5,6].</p> <div style="display: flex; justify-content: space-around; align-items: center;"> </div>	<h3>4. Results</h3> <h4>Cumulative measure</h4> <p>Greater cumulative measure score in the mother-reared compared to nursery-reared group</p> <h4>Computational model</h4> <div style="display: flex;"> </div> <p><b>lambda1</b> nursery-reared faster rate of working memory decay  <b>lambda2</b> nursery-reared longer-lasting tendency to repeat their previous choice  <b>beta</b> nursery-reared more random in their responses.</p> <div style="display: flex;"> </div>
<h3>2. Project objectives and subjects</h3> <h4>Objectives</h4> <p>Investigate the effect of early social deprivation on the development of EF in adolescent rhesus macaques</p> <h4>Subjects</h4> <p>2 groups of rhesus macaques          - mother-reared MR (11)          - nursery-reared NR (10)</p> <div style="display: flex; justify-content: space-around;"> </div>	<h3>4. Analysis</h3> <p>A. CUMULATIVE MEASURE = <math>\frac{\text{addition of correct change trials delays}}{\text{number of total trials}}</math></p> <p>B. COMPUTATIONAL MODEL</p> <div style="display: flex; justify-content: space-around;"> </div> <div style="display: flex; justify-content: space-around;"> </div>	<h3>5. Conclusion</h3> <p>These are the first results to demonstrate that, like in humans, early social adversity is associated with poor executive function in young rhesus macaques, with the computational model providing novel insights into the neural mechanisms through which this may occur.</p> <h4>References</h4> <ol style="list-style-type: none"> <li>Willcutt et al., 2005. Biol Psychiatry, 1:5711:1336-46.</li> <li>Karalunas et al., 2018. J Abnorm Child Psychol, 46(8):1705-1716.</li> <li>Wade et al., 2019. PNAS, 116(5):1808-1813.</li> <li>Golm et al., 2020. Psychol Med, 18:1-10.</li> <li>Diamond et al., 1989. Exp Brain Res, 74(1):24-40.</li> <li>Holmboe et al., 2018. Dev Sci, 21(6):e12690.</li> </ol>

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# Poster presented at the International Society for Developmental Psychobiology conference (2021)

The work on which this poster is based has now been published (Rayson et al., 2021). The manuscript is presented in Appendix A of this thesis.

## Early social adversity influences the relationships between attention biases and socioemotional behaviour in juvenile macaques

H. Rayson<sup>1</sup>, A. Massera<sup>1</sup>, M. Belluardo<sup>2</sup>, S. Ben Hamed<sup>1</sup>, & P.F. Ferrari<sup>1,2</sup>

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### 1. Introduction

**Affect-biased attention** thought to play a fundamental role in early socioemotional development<sup>1</sup>

- But **mechanisms and links to typical<sup>2</sup> vs. adverse<sup>3</sup> outcomes** unclear

Important question:

- What factors lead to **individual differences** in affect-biased attention and risk/resilience?

**Macaque model** may be particularly useful to address these questions

- But do similar attention biases to humans exist in macaques and do they relate to socioemotional function?

### 2. Subjects and Tasks

**Subjects**

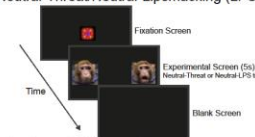
21 juvenile rhesus macaques

- 11 mother-reared (MR)
- 10 peer-reared (PR)
- ~2.5 years of age/pre-adolescent

**Attention Bias Task**

2 conditions (dynamic stimuli):

- Neutral-Threat/Neutral-Lipsmacking (LPS)



**Behavioural Observation**

Videos made of subjects in home enclosure to assess socioemotional function

### 3. Data Acquisition and Analysis

**Procedure and Video Coding**

**Attention bias task:**

- Subjects separated into testing area
- 87 × 100 × 120cm with clear-pannelled front
- Screen placed outside 60cm from front

**Calibration**


- Object+sound presented left/centre/right of screen

**Stimuli presentation**

- 5 Neutral-Threat & 5 Neutral-LPS trials
- Subjects recorded via webcam

**Gaze coding**

- Gaze during stimuli presentation coded offline (left/centre/right/other/offscreen)



**Behavioural observation:**

Subjects housed in mixed MR/PR social groups

Total 30 minutes observation per subject over three weeks

**Socioemotional behaviour coding<sup>4,5</sup>**

- Anxiety-like behaviour identified (frequency)
- Involvement in grooming interactions identified (frequency and duration)

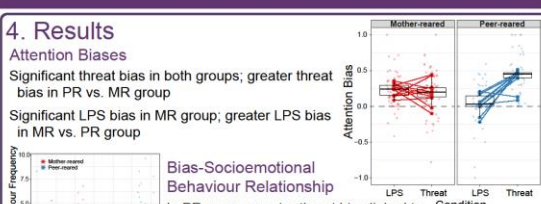
**Statistics**

Mixed model framework: linear model (gaze bias), generalized linear model - negative binomial with log link function (behaviour)

### 4. Results

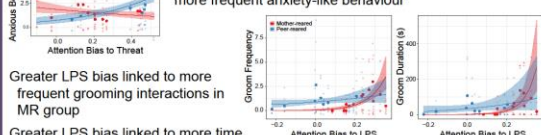
**Attention Biases**

- Significant threat bias in both groups; greater threat bias in PR vs. MR group
- Significant LPS bias in MR group; greater LPS bias in MR vs. PR group



**Bias-Socioemotional Behaviour Relationship**

- In PR group, greater threat bias linked to more frequent anxiety-like behaviour



- Greater LPS bias linked to more frequent grooming interactions in MR group
- Greater LPS bias linked to more time spent in grooming interactions across groups

### 5. Summary and Conclusions

**Differences in attention biases between groups**

- Threat bias greater in PR group
- LPS bias greater in MR group

**Greater threat bias linked to more frequent anxiety behaviour in PR group**

**Greater LPS bias linked to more affiliative behaviour in both groups**

**Results similar to those with human children in context of early institutionalization<sup>6,7</sup>**

**Results indicate utility of macaque model for future developmental affect-biased attention research**


**References**

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# Poster presented at the Federation of European Neuroscience Societies (2022)



A manuscript based on the work presented in this poster is currently in preparation. All work involving resting-state fMRI was led by Suliann Dr Ben Hamed; Simon Clavengier, with the help of Mathilda Froesel, preprocessed and analysed the data; both Mathilda Froesel and Maeva Gacoin were involved in all MRI data acquisition, under the supervision of Dr Ben Hamed.



9-13 July 2022 | Paris, France

## Early social adversity in non-human primates interferes with the developmental trajectory of amygdalo-cortical functional connectivity

Simon Clavagnier\*, Holly Rayson\*, Mathilda Froesel\*, Maëva Gacoin, Alice Massera, Pier Francesco Ferrari, Suliann Ben Hamed

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### Introduction

Neuroimaging of the non-human social primate brain has been instrumental to forge our current understanding of primate social cognition. However, little is known to date on how this cognitive function develops from childhood into adolescence, and how early social adversity (ESA) interferes with typical brain functional developmental trajectories. Here, we used a longitudinal neuroimaging protocol and collected anesthetized resting-state fMRI data in 21 juvenile monkeys.

We focus on the amygdala, a subcortical structure which plays a key role in socioemotional and attentional processing.

### Material and Methods

3T Resting state MRI acquisitions under anesthesia + MION injection

**Control group** : 11 **Mother-reared (MR)** macaques  
**ESA group** : 9 **Peer-reared (PR)** macaques (Rayson et al, 2021)

**3 Time points** : - Childhood (age 1: 2.63y +/- 0.06)  
 - Adolescence (age 2: 3.75y +/- 0.2)  
 - Early adulthood (age 3: 4.9y +/- 0.23)

**MRI anatomical procedure**

- 2 T1w + 1 T2w whole brain images
- Processing method using Matlab, AFNI, FSL, Freesurfer, ANTs and Connectome workbench (Adapted from Autio et al, 2020 and Seltitz et al, 2017)

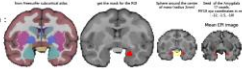
**Resting state MRI procedure**

- 4 runs of 526 EPI images (28 slices, 1.5x1.5x1.6mm, TR = 1.7s, TE = 17ms)

Processing method (using Matlab, AFNI and FSL)

- Despiking - Slice time correction - Motion correction - Bias field correction
- Non linear transformation to the individual reference T1w image and Skull-stripping
- Non linear transformation to MNI154 atlas
- Detrend - bandpass filter (0.01-0.1Hz), censoring - Regressing out head motion, mean white matter signal and mean ventricles signal
- Blurring at 3 mm - Signal normalisation
- Hand classification and removal of ICA noise component with MELODIC

**FC Analysis** :  
 Left and Right Amygdala :



**Seed-based correlation analysis** per each run + Fisher's-to-Z score transformation

- T Test.
- "Right-to-left" transformation of Right Amygdala results.

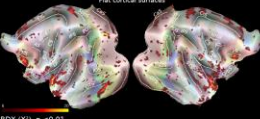
**Linear Mixed-Effects Modelling Approach** analysis

Random intercept and random slope : Age x Group + (1/Monkey)

Random effects (RDX) : AGE, GROUP and AGExGROUP

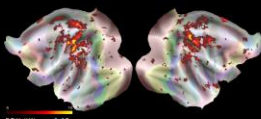
### Results

**AGE effect**



RDX (X), p < 0.01

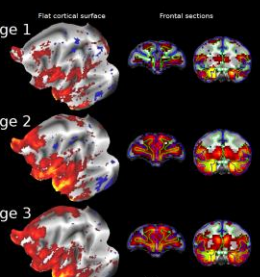
**GROUP effect**



RDX (X), p < 0.05

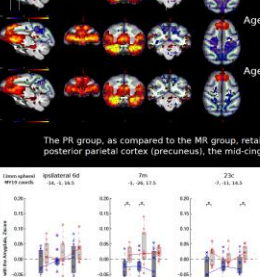
mean Zscore per age (inclusive mask from "FX all ages" FDR q<0.001)

**MR group**

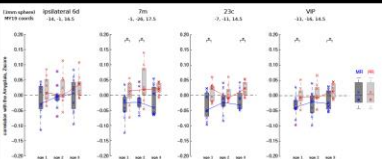


Fixed effect (FDR q<0.001)

**PR group**



The PR group, as compared to the MR group, retains part of its functional connectivity with the medial posterior parietal cortex (precuneus), the mid-cingulate and specific premotor and prefrontal regions.



**ROI analysis**

Variability within the groups relation with individual attentional and/or social disabilities ?

=> node-based analyses

refinement of the amygdalo-cortical connectivity through adolescence, from a broad distributed pattern to a more adult-like restrained pattern.

No interaction between the two main effects

**Conclusion**

We propose that altered amygdalo-cortical functional connectivity in the peer-reared group accounts for the specific differences in affect-biased attention and high emotional reactivity observed in this group.

Rayson et al. "Early social adversity modulates the relation between attention biases and socioemotional behaviour in juvenile macaques." Sci Rep. 2021  
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