Divergent developmental trajectories of threat-related regional brain metabolism across the first year of life in rhesus monkeys

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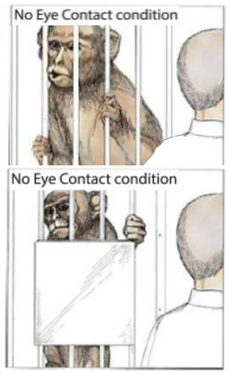
Objective: *Characterize the early-life developmental trajectories of threat-related brain metabolism, and as they relate to Anxious Temperament*

1.Background

Postnatal Brain Development

During infancy, human and nonhuman primates (NHPs) experience rapid and robust development in the central and peripheral nervous system. The brain undergoes cortical expansion, myelination, and organization/integration of critical neural circuitry. Prior work[1] demonstrates that resting brain glucose metabolism as measured by ^{18}flurodeoxyglucose- Positron Emission Tomography (^{18}FDG-PET) generally increases across grey matter during this period, while glucose metabolism in white matter decreases. Here we expand on this by examining the developmental trajectories of **threat-related** brain metabolism during the first year of NHP life.

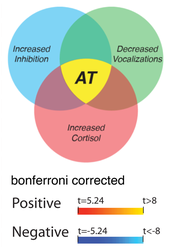
Anxiety responses in young nonhuman primates (NHPs)



Anxiety responses in rhesus macaques (*maccaca mulatta)* are characterized with the Human Intruder Paradigm (HIP), where a monkey is placed in a novel testing cage and exposed to various contexts that trigger distinct behavioral responses. During the No-Eye-Contact condition (NEC), an unfamiliar intruder enters and presents their profile to the monkey. This exposure to a potential threat triggers the monkey to respond with behavioral inhibition by freezing and suppressing vocalizations[2]. While this response is innate, trait-like, and stable within individuals[4], it is not maturely expressed in early infancy[3]. This delay in mature expression may be due in part to changes in brain function during postnatal development.

Figure 1.1[2] – examples of stress responses to NEC, vocalizing (top) and freezing (bottom)

NEC-related brain function in preadolescent NHPs



In 592 monkeys, after receiving injection of ^{18}flurodeoxyglucose (^{18}FDG) followed by 30 minutes of NEC, associated brain function was visualized with Positron Emission Tomography (PET). Anxious Temperament (AT) scores were computed from behavioral expression during NEC, and subsequent blood cortisol levels. This study found that individual differences in AT predict individual differences in NEC-related brain metabolism.[4]

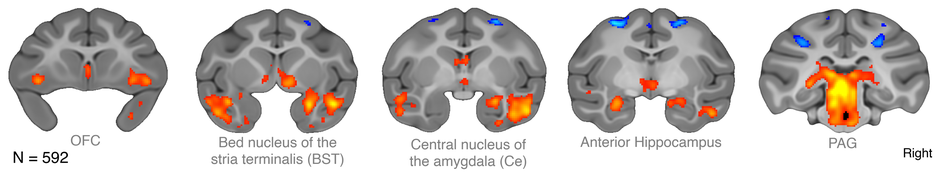


Figure 1.2 – monkeys with higher AT have increased activation of limbic regions during NEC[4]

2.Methods

Study Description

During their first year of life, 35 NHP rhesus macaques (24F/11M) were tested longitudinally with anxiety assessment and multimodal imaging. Anxiety-related brain function was measured 5 times with ^{18}FDG-PET scans following 30 minutes of NEC from the HIP.

Image processing

At 5 ages between birth and 1 year, injection of ^{18}FDG was followed by 30 min of NEC. Animals were then anesthetized under veterinary care and placed in a μPET scanner for imaging. One week later, animals underwent structural and functional MRI scans. The 5 MRI scans for each subject were first co-registered within subjects, and then across subjects in ANTS to create an overall population template. This template was then warped into a standard NHP template space constructed from 592 animals[4]. ^{18}FDG-PET images were scaled to whole-brain activity levels, co-registered to the population template, and smoothed. Within subject linear mixed effects models were run voxel-wise on individuals subjects' imaging data. Age-related voxel-wise analyses were visualized at $p<2.2x10^{-8}$, which corresponds to a p=0.05 threshold, Bonferroni corrected. Voxel-wise analyses investigating main effects of AT and its interaction with age were visualized at p<0.005, uncorrected. All imaging and statistical analyses were conducted while controlling for possible effects of gestation length and sex. AT-related analyses were run while accounting age-related effects.

Full Project Timeline

35 NHP (24F/11M)

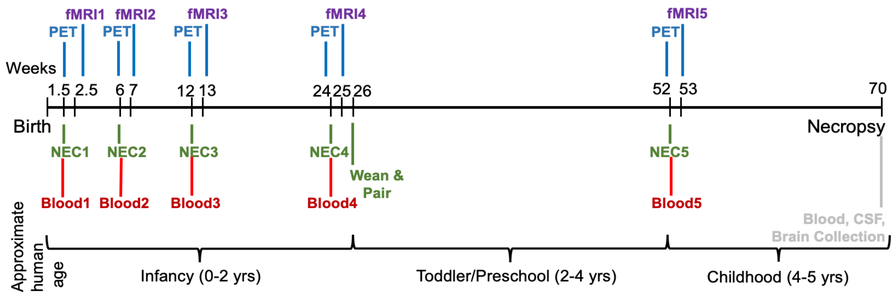


Figure 3.1 – Timeline of longitudinal testing, approx. translating to first 4 years of human postnatal development. NHPs were tested 5X with 30 min of NEC with ^{18}FDG-PET imaging.

3.Results

Age-related AT Trajectory

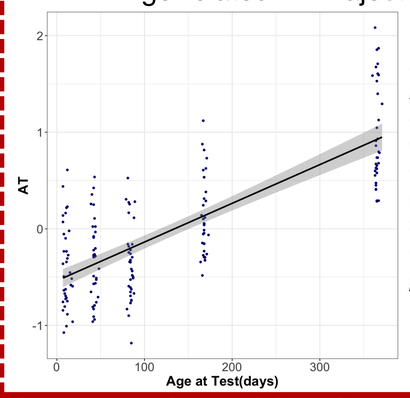


Figure 3.2- AT increases linearly within subjects during the first year of life $p< 2.0x10^{-16}$

Summary table of ROIs from voxel-wise analyses of threat-related brain function

ROIs in significant clusters from analyses with:		
Age	AT	AT x Age Interaction
p<2.2x10-8	*p<0.005*	*p<0.005*
dlPFC (+)	**BST (+)**	**MST, TPO (-)**
OFC (+)	**Caudate (+)**	**V3A, V6, PO (left) (-)**
pOFC (+/-)	**Thalamus (+)**	**V3A, V6, PO (right) (-)**
CC (+/-)	**TPO, TEa, PGa, Ipa (-)**	posterior hippocampus
Amygdala (-)	Area 23	PGa, IPa
BST (-)		**primary visual (V1) (-)**
Insula (+)		ECL, 35, 36R
Basal Ganglia (+)		TPO, TEA
Thalamus (-)		pOFC (48 voxels)
Cerebellum (-)		
Primary Visual (-)		
Higher Order Visual (+/-)		

Table 1 – bolded regions visualized in more detail below, + indicates positive relationship, - indicates negative

Longitudinal age-related changes in threat-related brain metabolism over the first year of life

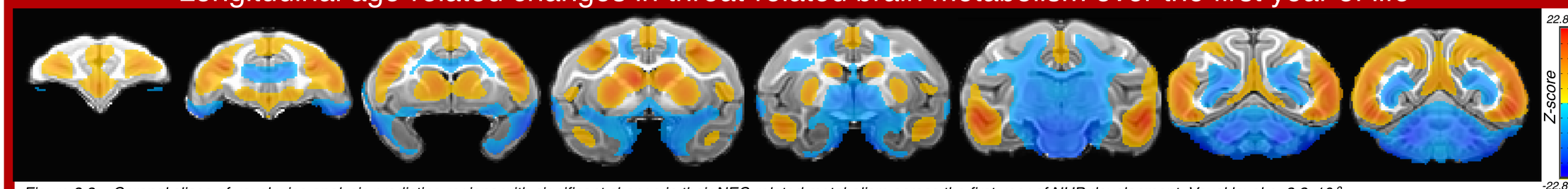


Figure 3.3 – Coronal slices of voxel-wise analysis predicting regions with significant change in their NEC-related metabolism across the first year of NHP development. Voxel level $p<2.2x10^{-8}$

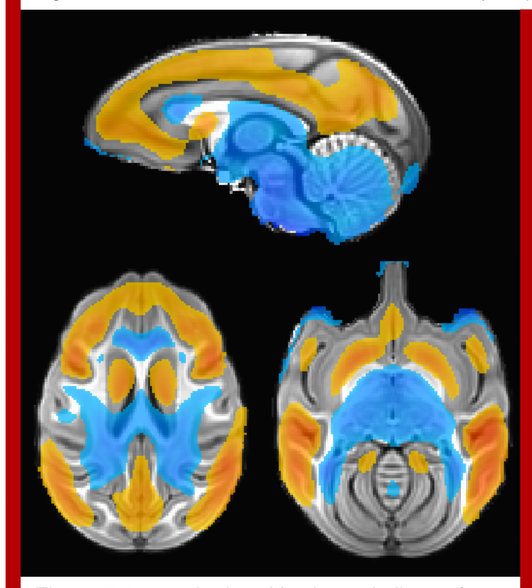


Figure 3.4 – sagittal and horizontal slices of analysis depicted in 3.3. Voxel level $p<2.2x10^{-8}$

Threat-related brain metabolism in relation to AT over the first year of life

Main effect of AT across year 1

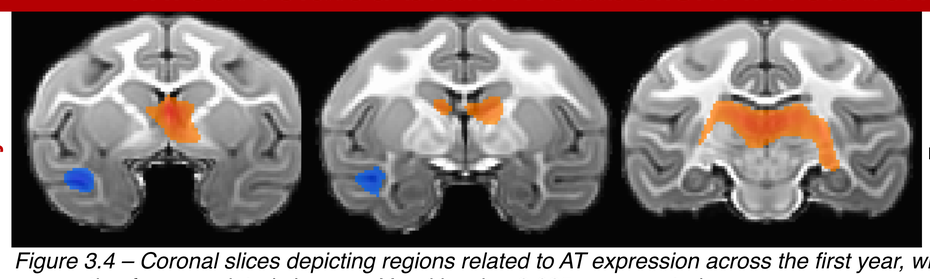


Figure 3.4 – Coronal slices depicting regions related to AT expression across the first year, while accounting for age-related changes. Voxel level p<0.005, uncorrected

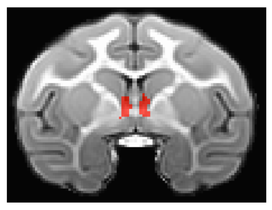


Figure 3.5 – Calabrese defined BST ROI used to extract values for BST plot

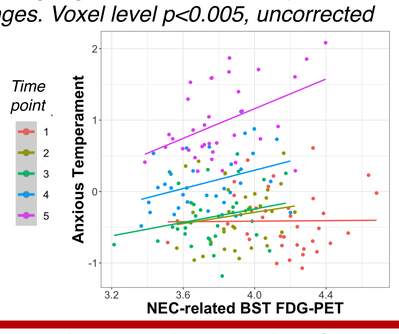
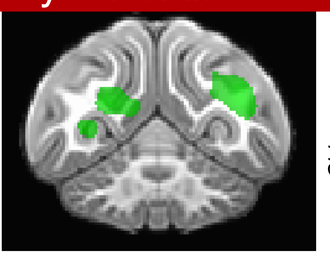


Figure 3.6 – (left) individual data points for BST threat-related metabolism as it relates to AT across the first year, p=0.0011

Age x AT interaction during year 1

Figure 3.7 – (right) clusters in visual regions (V1, MST, V3/PO) with significant Age x AT interaction, p<0.005



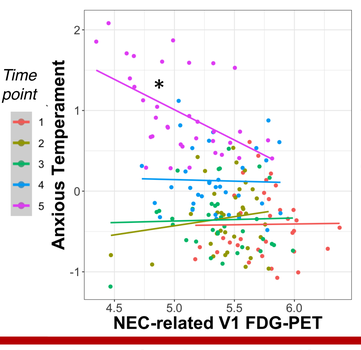


Figure 3.8 - (left) individual points from V1 cluster with significant Age x AT interaction across the first year, p=0.0018. By T5, greater V1 metabolism during threat is associated with lower AT, (p=0.002) similar to what is observed in older NHPs[4]

4. Implications

Threat-related metabolic activity in cortical regions increases with age during the first year of NHP life. In contrast, reductions in threat-related metabolism are generally observed in subcortical regions. BST metabolism is associated with individual differences in AT across the first year of life.

References

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