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Exploring the neural substrates for emotion regulation and psychopathology in non-human primates.

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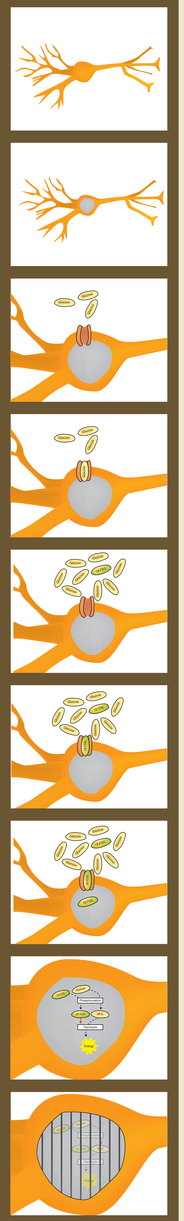
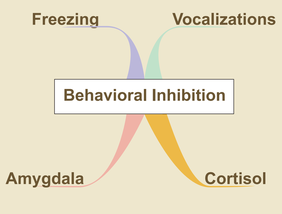


Review of Behavioral Inhibition

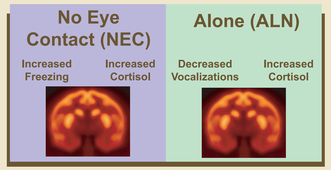
Human Children:
- Increases in freezing behaviors
- Increased levels of basal cortisol
- Increases in right frontal brain asymmetry
- Increased amygdala responsivity to novelty in early adulthood
- Decreased number of spontaneous vocalizations

Rhesus Monkeys:
- Increased duration of freezing behaviors
- Increased levels of basal cortisol
- Increases in right frontal electrical brain activity
- Increased metabolic activity in the amygdala (p<.05, two-tailed uncorrected)
- Central Amygdala Lesions decrease freezing behavior
- ???
- Amygdala Metabolism is negatively related to the frequency of coo vocalizations
- Central Amygdala Lesions increase coo vocalizations

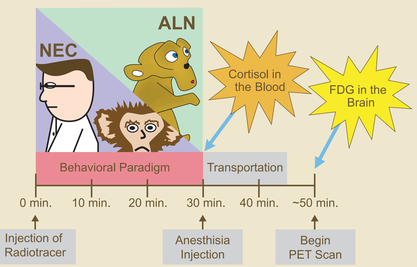
Theoretical Model:
Facents of Behavioral Inhibition



Context Elicited Markers of Behavioral Inhibition



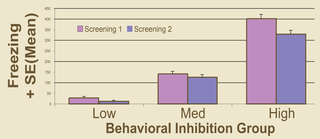
FDG PET Paradigm



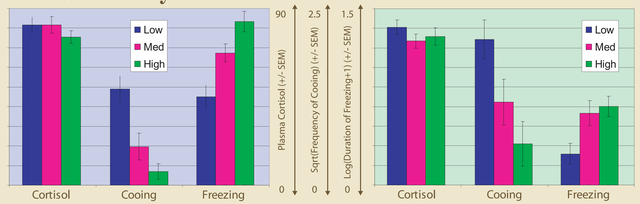
After identification of the 3 groups of animals, each monkey underwent two [18F]-fluoro-2-deoxy-D-glucose (FDG) PET scan to investigate the integrated neural activity associated with non-specific threat (NEC) and separation from their partner (ALN) into a test cage. These two consitions were selected becase they elicit freezing and cooing, which are associated with behavioral inhibition, respectively. FDG, which has a ~110 minute half-life, was administered immediately prior to the 30 min separation period after which the monkeys were anesthetized and scanned.

Modeling Psychopathology: Definition of Groups

Three groups of monkeys (High n=11; Med n=12; Low n=12) were selected from 117 animals based on their propensity to be stably behaviorally inhibited, as measured by their amount of freezing when presented with the profile of a human intruder (NEC; Kalin & Shelton, 1989).



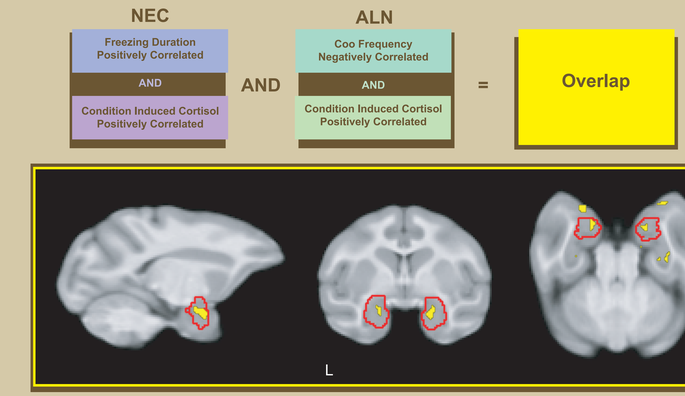
Behavioral Analysis

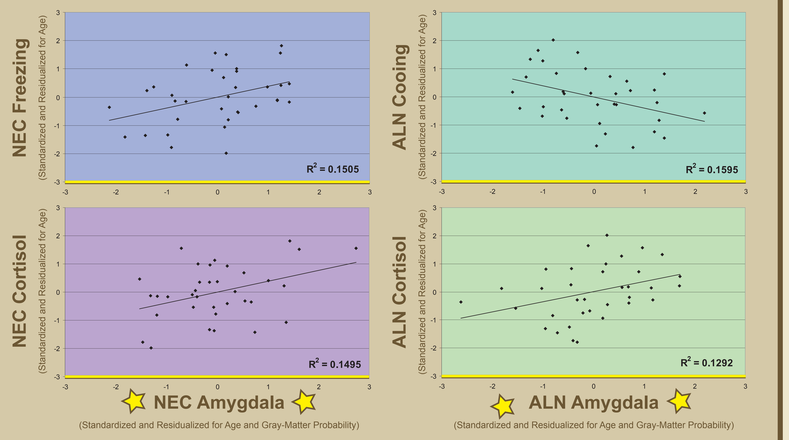


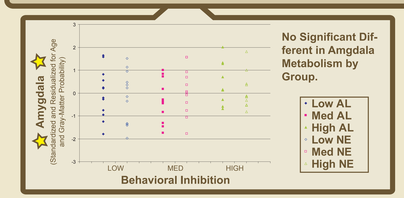
During NEC we observed significant differences in Freezing F=13.061, p<.001) and cooing (F=12.581, p<.001), but not cortisol (F=.890, p=.420). During ALN we observed significant differences in Freezing F=5.148, p=.012) and cooing (F=5.882, p=.007), but not cortisol (F=.857, p=.434).

Correlating Behaviors: In this sample Freezing during NEC and Cooing during ALN are negatively correlated (r = -.42, p = .013). We fail to find significant correlations between: Freezing during NEC and Cortisol during NEC (r = -.19, n.s.), Cooing during ALN and Cortisol during ALN (r = -.18, n.s.), as well as between Cortisol during ALN and Cortisol during NEC (r = .158, n.s.).

Conjunction Analysis: Overlap of four separate voxelwise correlations between markers of behavioral inhibition and FDG in the Brain when controlling for age and gray matter probability. Yellow regions represent areas consistently significant (p<.05, two-tailed uncorrected) across all four voxelwise tests.







No Significant Different in Amgdala Metabolism by Group.

- Low AL
- Med AL
- High AL
- Low NE
- Med NE
- High NE

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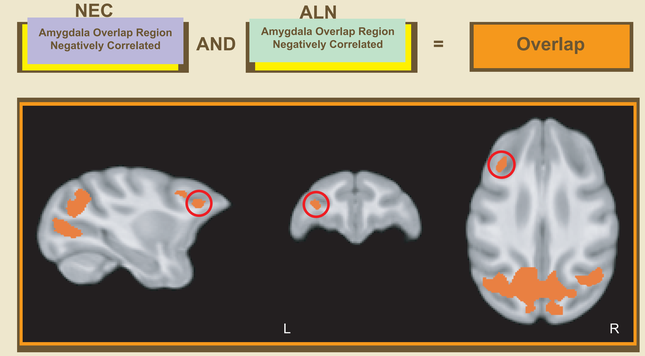
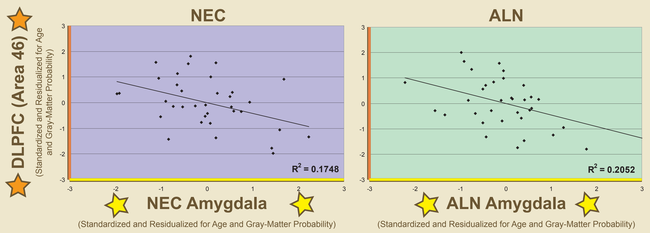
Exploring Emotion Regulation:

While it has been suggested that behavioral inhibition may in part be due to alterations in self-regulation, no research has explored the neural basis for alterations in the regulation of emotion hypothesized to underlie behavioral inhibition. Recent evidence suggests that the projections from the ventral-medial prefrontal cortex (VMPFC) to the amygdala may in part underlie the ability to regulate fear and anxiety related responses (Quirk et al., 2000; Quirk et al., 2003; Kim et al., 2004; Urry et al., 2006). The initiation of the VMPFC regulatory effects has been further suggested to involve the recruitment of dorsal-lateral prefrontal cortex (DLPFC; areas 46/9) and the anterior frontal pole (Area 10) (Davidson, Fox, & Kalin, 2007; Johnstone et al., submitted; Kim et al., 2004; Urry et al., 2005).

Conjunction Analysis: Overlap between voxelwise correlations between FDG in the Amygdala and FDG in the rest of the Brain across the ALN and NEC conditions when controlling for age and gray matter probability. Orange areas represent areas significantly (p<.005, two-tailed uncorrected) negatively correlated with the amygdala in both contexts.





Conclusions

In addition to increases in freezing behavior, decreases in cooing vocalizations appears to be characteristic of behaviorally inhibited animals. This may be analogous to the decreases in spontaneous vocalizations observed in behaviorally inhibited children. These imaging findings provide evidence that the behavioral and endocrine features of behavioral inhibition share a common substrate, the amygdala. In previous studies examining the effect of CeA lesions we found decreases in freezing and cortisol along with increases in cooing.

Since the amygdala is known to be modulated by prefrontal systems, we investigated the extent to which prefrontal regions predicted amygdala activity. Across the NEC and ALN contexts DLPFC was related to amygdala activation. This suggests that the interactions between amygdala and DLPFC are important in determining individual differences in behavioral inhibition.