

## Imaging fear stress responses in monkeys.

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### Introduction

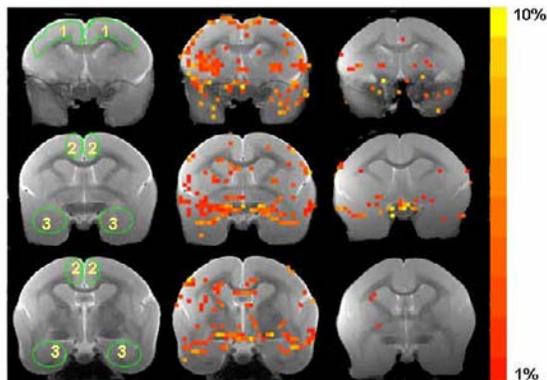
Unconditioned fear (fear that is innate or unlearned) occurs in response to threatening situations, such as the presence of a predator. Many mammalian species react to predation with remarkably similar behaviors, and cross-species studies that examine the mechanisms underlying the fear response are important for improved understanding of human fear. Unconditioned fear in humans underlies phobias and has importance for other psychiatric conditions; furthermore, unconditioned fear is known to increase with aging. We have previously studied the rodent behavioral and fMRI response to predator odor in the form of fox scent. These data demonstrate that a similar fMRI response occurs in small primates exposed to the odor of bobcat urine.

### Methods

3 old and 3 young (adolescent) male common marmoset monkeys (*Callithrix jacchus*) were acclimated to a restraint system that allows us to image conscious animals (Insight Neuro-Imaging Systems, MA, USA) and incorporates surface and volume coil electronics. Acclimated marmosets were imaged on a 4.7T Bruker small animal magnet. Imaging included an anatomical scan (RARE, 3.5cm field of view, 16 axial slices, 1.5mm thick and 2mm interslice distance, resolution 256x256, repetition time 2000msec, effective TE 48.8msec, echo time 12msec, rare factor 8, 8 averages, 180° flip angle), followed by a functional scan (spin echo EPI, resolution 64x64, TE effective 27.5msec, TE echo time 55msec, TR 4000msec, excitation pulse length 3000μsec, 90° flip angle). Functional data were recorded before the marmosets were exposed to the scent, during scent exposure, and during return to baseline once scent was removed.

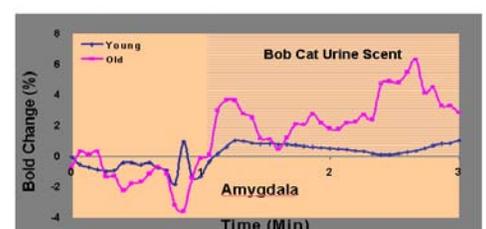
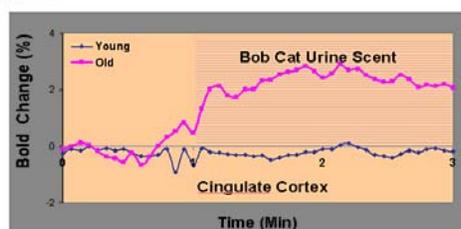
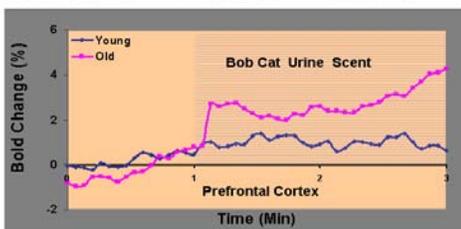
### Results

Fig 1 shows representative positive BOLD change maps from old and adolescent marmosets, whilst Fig 2 shows the time course of the BOLD response in the 3 main regions of interest, i.e. the prefrontal cortex, cingulate cortex and amygdala in the group data from 3 old and 3 adolescent monkeys. Old marmosets had a stronger response to bobcat odor than adolescent marmosets. Significant activation of the amygdala (associated with fear) and of the frontal cortices (which modulate the amygdala) was seen in response to the bobcat urine odor.



**Figure 1 (left): Representative positive BOLD responses to bobcat urine odor** (activation threshold  $p < 0.05$ , comparing baseline to scent exposure). Left panel shows ROIs: (1) prefrontal cortex, (2) cingulate cortex, and (3) amygdala. Middle panel shows typical response of old male marmoset. Right panel shows typical response of adolescent male marmoset.

**Figure 2 (below): Mean BOLD % change over time in brain areas associated with the fear response in 3 old and 3 adolescent male marmosets.** Left graph shows BOLD response in prefrontal cortex, middle graph shows BOLD response in cingulate cortex, right graph shows BOLD response in the amygdala. Odor was placed in the bore of the magnet at time point 1.



### Discussion

Elucidation of the mechanisms underlying unconditioned fear across mammalian species may assist in understanding phobias and aging-related increases in fear-related psychiatric disorders. Marmoset monkeys respond to the odor of a potential predator with “fearful” behavior (avoidance, trembling, warning vocalizations, crouching and flight). This study has demonstrated that brain areas associated with fear, namely the amygdala, prefrontal cortex and cingulate cortex, at least in older adult marmosets, all respond with significant activation when odor associated with a predator is present in the environment. The exaggerated response of aged marmosets, as compared to adolescent/young adults, suggests that the increase in unconditioned fear seen in older humans may occur in other species.