# FMRI evidence for HIV-induced acceleration of aging in middle-aged women

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## ABSTRACT

- Studies have shown that HIV-associated neurocognitive disorders (HAND) are more severe in older people with HIV disease than their younger counterparts, and it has been suggested that the increased vulnerability might be due to HIV-induced accelerated aging.
- In cognitive aging, it has been proposed that aging-related cognitive decline might be due to age-related neural dedifferentiation, i.e., a decreases in neural specificity, which precedes the onset of significant behavioral changes, as shown in recent functional magnetic resonance imaging (fMRI) studies of aging (*Goh et al., Neuroimage, 2010*). *Here we hypothesize that HIV-induced acceleration of aging will lead to a decrease in neural specificity in middle-aged adults, similar to those observed in older adults, probably due to synapse damage and/or increased neuronal noise.*
- In the present study, using two advanced fMRI techniques – fMRI rapid adaptation (fMRI-RA) and local regional heterogeneity (Hcorr) – both capable of measuring neural specificity more directly than conventional fMRI techniques, we directly tested this hypothesis.

## fMRI-RA

***functional Magnetic Resonance imaging - rapid adaptation***

A fundamental problem limiting the ability of conventional fMRI is that the average activation level observed in fMRI experiments may not necessarily reflects neuronal specificity – Because of the limited spatial resolution of fMRI, a particular mean voxel response could be obtained by a few neurons in that voxel which each respond unselectively to many different stimuli (low neuronal specificity), or by a large number of highly selective neurons which each respond only to a few stimuli stimuli (high neuronal specificity), yet these two scenarios have very different implications for behavioral discrimination ability.

In contrast, fMRI adaptation techniques have been shown to be able to more directly probe neuronal selectivity than conventional methods relying on average BOLD-contrast stimulus responses (*Grill-Spector et al., 2006*). The fMRI rapid adaptation technique (fMRI-RA) is motivated by findings from monkey electrophysiology experiments in ventral temporal cortex, reporting that the second presentation of a stimulus (within a short time period) evokes a smaller neural response than the first. It has been shown that this adaptation can be measured using fMRI, and that the degree of adaptation depends on stimulus similarity, with repetitions of the same stimulus causing the greatest suppression. Several studies have provided evidence that parametric variations in visual object parameters (shape, orientation, or viewpoint) are reflected in systematic modulations of the fMRI-RA signal, and can be used as an indirect measure of neural population tuning, i.e., neuronal specificity.

## $H_{corr}$

***the heterogeneity of local regional correlations***

Recently, we have introduced a novel technique, *local regional heterogeneity analysis, $H_{corr}$* to probe the sparseness of neuronal activation patterns and to provide a measure of neural specificity (*Jiang et al., Neuroimage Clinical, 2013*). This technique is based on analysis of voxel-wise correlations of fMRI activation patterns with an assumption that the sparsity of neural activations is related to neuronal selectivity: The highly selective neurons produce a sparse neural code, with each neuron responding to a very small set of stimuli. In contrast, less selective neurons respond to a greater number of stimuli, leading to greater overlap in responses among the neurons and less sparse representations. Thus, for a neural representation of objects or events, activation patterns should be sparser for a population with more sharply tuned neurons than more broadly tuned neurons. This then predicts that the sharply tuned population should have a higher degree of heterogeneity in neuronal correlations than the population with more broadly tuned neurons. *Thus, when measured with fMRI, tuning specificity in a brain region should correlate with the degree of sparseness, which in turn should correlate with the heterogeneity of correlations in the region, Hcorr.*

***Hcorr = standard error of correlations between voxels***

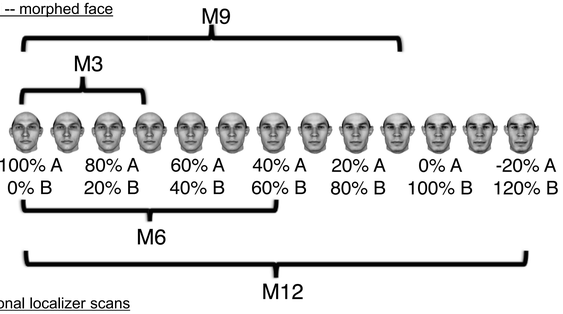
Therefore, a lower Hcorr should be associated with lower neuronal specificity, and a greater Hcorr with higher neuronal specificity.

## METHODS

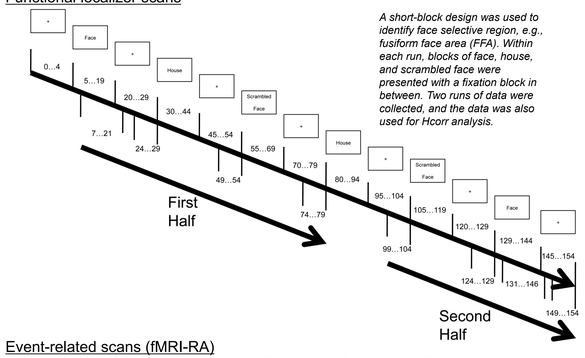
**Participants**: Twenty-nine middle-aged (43-59 years old) women with no major psychiatric disorders nor other confounding health problems (16 HIV-seropositive receiving HAART, 13 negative) recruited from the Washington DC site of the Women's Interagency HIV Study participated in this study. The two groups were matched in age, education, and socioeconomic status (SES). The Mini-mental status examination (MMSE) was used to screen for potential dementia.

**Experimental design**

- Stimuli -- morphed face



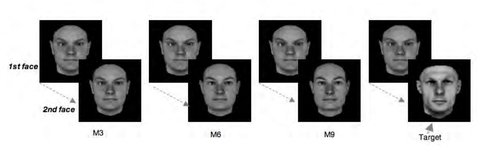

- Functional localizer scans




*A short-block design was used to identify face selective region, e.g., fusiform face area (FFA). Within each run, blocks of face, house, and scrambled face were presented with a fixation block in between. Two runs of data were collected, and the data was also used for Hcorr analysis.*

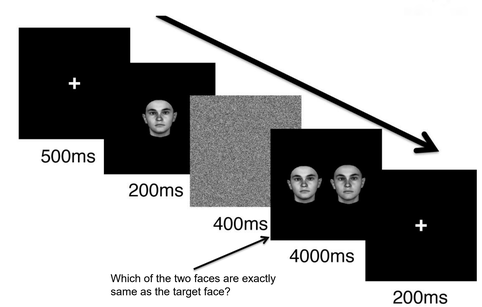
- Event-related scans (fMRI-RA)

*fMRI-RA was used to assess changes in neuronal specificity in subjects, with a focus on fusiform face area (FFA). Three conditions of interests were included (M3/6/9), along with an oddball task to ensure subjects were paying attention to stimuli. Three runs of fMRI data collected.*




- Psychophysics

*Subjects' face discrimination performance was assessed with a 2AFC paradigm, 4 morph steps (M3, M6, M9, and M12) were tested with both upright and inverted face.*

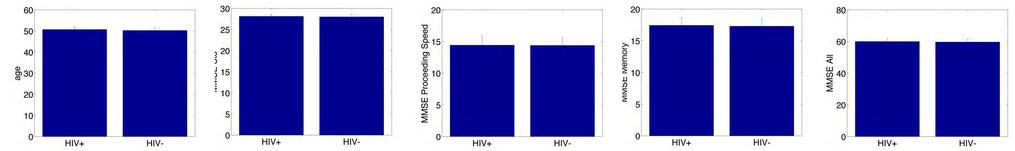



**MRI data acquisition.** MRI data were acquired using an echo-planar imaging (EPI) sequence on a 3.0 Tesla Siemens Trio scanner (Flip angle = 90° , TR=2.04s, TE=29ms, FOV=205, 64x64 matrix) with a twelve-channel head coil. Thirty-five interleaved axial slices (thickness = 4.0 mm, no gap; in-plane resolution = 3.2x3.2 $mm^2$) were acquired for the two functional localizer and three functional runs. At the end, three-dimensional T1-weighted MPRAGE images (resolution 1x1x1 $mm^3$) were acquired from each subject.

## RESULTS AND DISCUSSION

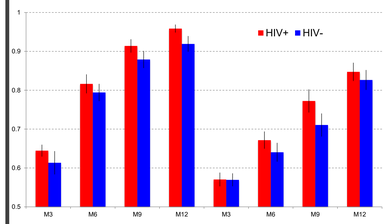
### DEMOGRAPHICS & MMSE

***(no group difference)***



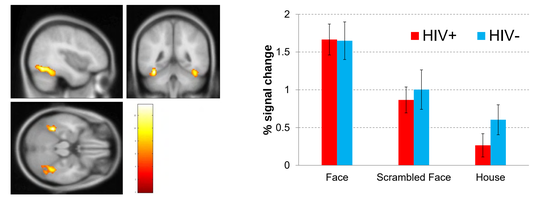

### PSYCHOPHYSICS

***(no group difference)***



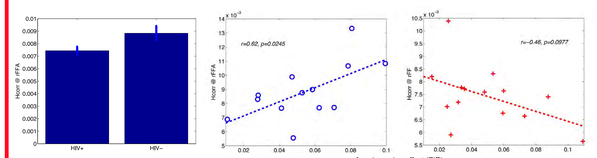

### CONVENTIONAL fMRI

***(no group difference)***



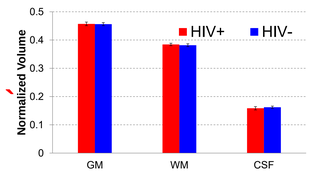

### Hcorr

***(HIV+ < HIV-, p<0.05)***



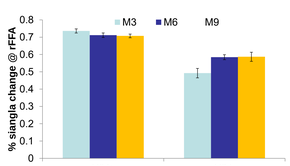

### VBM

***(no group difference)***




### fMRI-RA

***(adaptation: HIV+ < HIV-, p<0.05)***




### DISCUSSION

While behavioral and conventional MRI techniques failed to identify subtle neuronal dysfunction in asymptomatic HIV+ patients, two advanced fMRI techniques, fMRI-RA and Hcorr, revealed a decrease in neuronal specificity in HIV-positive patients, suggesting an age-related neural dedifferentiation due to the acceleration of aging, similar to those observed in cognitive aging, providing a direct support to the accelerated aging theory.

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