

Differences in Neuronal Responses due to Aging

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Introduction

Human aging is associated with the decline of many human abilities such as cognitive abilities. It is still unknown how much of cognitive decay is due to pathological reasons and how much is a direct consequence of normal aging. There are some studies indicating that aging causes changes in the brain and in one's neuronal responses. However, other experiments show that there is no relationship between age and neural changes.

One way of looking at neural activity is to use functional magnetic resonance imaging (fMRI) to examine the blood-oxygen level-dependent (BOLD) signal. Since fMRI imaging is safe, noninvasive, and has better resolution and spatial localization than other imaging techniques such as EEG (electroencephalogram) and PET (positron emission tomography), it is the preferred method in mapping neuronal responses. The BOLD mechanism tracks changes in cerebral blood volume, cerebral blood flow, and oxygen consumption to detect neural activation. In response to activation, more oxygenated blood flows to the area of activation, decreasing the ratio of deoxygenated to oxygenated hemoglobin in that area and increasing its BOLD signal (Logothetis & Wandell, 2004).

A problem with the BOLD response is that both age and disease can affect the integrity of the hemodynamic (amount of blood flow) response (Nielson et al., 2004). Aging causes a decreased signal-to-noise ratio in the BOLD signal and a reduction in both the signal amplitude and the number of activated voxels (the 3D equivalent of a pixel) within the sensorimotor cortex. Cerebrovascular diseases, such as strokes, cause a decrease in the rate of rise and maximal BOLD hemodynamic response function (HRF) (D'Esposito, Deouell & Gazzaley, 2003). Since there are additional factors that affect the BOLD signal besides age, fMRI is not a flawless method of tracking age-dependent changes in the brain.

Many studies have been conducted to identify the role that age plays in neural activity. Some scientists believe that neural responses do in fact correspond with age. Scott Huettel and researchers at Duke University Medical School used checkerboard stimuli to influence the hemodynamic response. They found that young people had twice as many activated voxels and reached peak activation later than the older participants, but the hemodynamic responses had a similar onset time, rate of rise, and peak amplitude in both groups (Huettel et al., 2001). Other studies also show that prefrontal activation is similar for both groups, but older people tend to have greater deep gray matter activation. Older adults place greater emphasis on the attentional control of response regulation since their task performance is more influenced by deep gray matter structures (Madden et al., 2004). These studies show a clear correlation between aging and brain response.

Other studies suggest that aging only affects certain parts of the brain, primarily the prefrontal cortex. Researchers at the National Institute of Aging reported that older participants performed more slowly in their tasks and also had greater activation in the prefrontal cortex during location matching, suggesting that aging affects spatial vision (Grady et al., 1994). Calautti and his colleagues also found that older people had more activation in the superior frontal cortex, hinting that older people treat stimuli as more complex. Furthermore, younger people had higher perfusion in anterior brain regions, allowing them to have less activation in those areas. Aging causes a decline in the resting-state brain perfusion and glucose consumption that leads to the need for more control during tasks, which in turn increases prefrontal cortex activation (Calautti et al., 2001).

In addition, there are studies showing that neural changes have very little correlation with aging. Dr. McConnell recorded that aging causes no significant change in motor threshold, percent signal change, and volume of activation produced by transcranial magnetic stimulation (TMS), a noninvasive method of using changing magnetic fields to excite neurons in the brain. His study suggested that age-related increases in the BOLD signal during tasks might actually be secondary to changes in the peripheral systems. In addition, he argued that cortical physiology does not actually decline with normal aging (McConnell, 2003). Dr. Nielson also found that old and young adults had similar hemodynamic responses, thus suggesting that differences in activation during cognitive inhibition are not due to vascular coupling. Instead, some researchers blamed the differences in BOLD responses on less-significant or negative voxels. The elderly have a greater percentage of negative voxels in the visual region, suggesting that they may have more unconstrained visual processing (Aizenstein et al., 2004).

Different studies have divergent findings on neuronal differences between older and younger adults. Since this issue is important in learning more about the effects of aging on the human brain and its mental capabilities, the present study was conducted similarly to previous studies in order to compare the results. In this experiment, different stimuli were simultaneously presented to college students and older adults. Using BOLD fMRI imaging, the participants' brain activation levels were recorded via their hemodynamic responses. Scans were performed in two different sessions to ensure reliability. By comparing data such as the time to reach activation peaks and the amount and length of activation, the extent to which aging affects the human brain would be better understood.

Methods

Participants:

Stanford University's Internal Review Board (IRB) approved this experiment before it was conducted. Twelve young individuals (8 males, 4 females, 18-28 years old) and twelve elderly individuals (7 males, 5 females, 65-75 years old) recruited from Stanford University and the surrounding communities voluntarily participated in this study. All gave informed consent and reported no neurological or psychiatric

disorders, drug abuse, or other abnormalities that might distort the results. Functional MRI conducted on a 3.0-Tesla GE scanner (General Electric Medical Systems Signa, Waukesha, Wisconsin) paired with a whole-head coil was used to detect neural activation in the participants' brains when presented simultaneously with visual, motor, and auditory stimuli. Flashing checkerboard patterns and a sequence of ascending and descending tones were presented concurrently to them while they tapped their fingers. Head movement was minimized with a bite-bar. They were each scanned twice to make sure the results were consistent and therefore reliable. The scanning took approximately an hour and the participants had to return after two weeks for the second scan. Functional data consisting of 220 volumes used an interleaved T2*-weighted spiral in-out acquisition sequence to measure the BOLD response (TR = 1500ms, TE = 30ms, flip angle=70°, FOV=24, 64 x 64 matrix). Twenty-two axial-oblique slices of 5mm thickness were acquired parallel to the AC-PC line and covering the whole brain. Co-planar and high-resolution T1-weighted volumes were collected for each subject.

Preprocessing:

The first step of the analysis involved preprocessing the raw functional images using Matlab. The first 4 images were dropped to allow for equilibrium to be reached in the magnetic field. The orientation and appearance of both the anatomical and functional images were checked for any irregularities. Next, a time course for global signal and its relation to movement was plotted to make sure that no signal changes were more than 1.5% or above 4 standard deviations (SDs) and that the range of mean signal was less than 50. This ensured that the signals were relatively constant and did not correspond with movement.

After making sure that there were no clear artifacts, the data was slice timed to correct for different slices of the brain being collected at slightly different times. Then the images were coregistered to align the first functional images of the two scan sessions. The first anatomical image was then coregistered with the first functional image of the first scan to make sure that the anatomical images were aligned with the functional ones. Next, the images were transformed again through normalization to match the first anatomical and first functional images with that of the Montreal Neurological Institute's (MNI) brain template to ensure that everything was well aligned. The functionals from the two scans were also normalized to align with the first anatomical. The last step of the preprocessing involved 6 mm smoothing of the functional images in both scan sessions to blur the data and increase the signals.

HRF Estimation:

After the preprocessing, the images for both scan sessions were reviewed to make sure that there was activation in regions of the brain corresponding to the stimuli presented to the participants. Since motor, auditory, and visual stimuli were presented to the two groups, activation in the left and right motor, auditory (temporal), and visual (occipital) regions of the brain was expected and confirmed in all the participants. Then, the timecourses of each region of interest (ROI) for every individual were extracted.

Regions of Activation

Cluster Size	Region	MNI Coordinates (x, y, z)
226	Left Motor	(-51, -27, 51)
210	Right Motor	(45, -18, 57)
149	Left Auditory	(-54, -18, 0)
133	Right Auditory	(69, -21, 0)
555	Left Visual	(-12, -90, -9)
	Right Visual	(6, -87, -6)

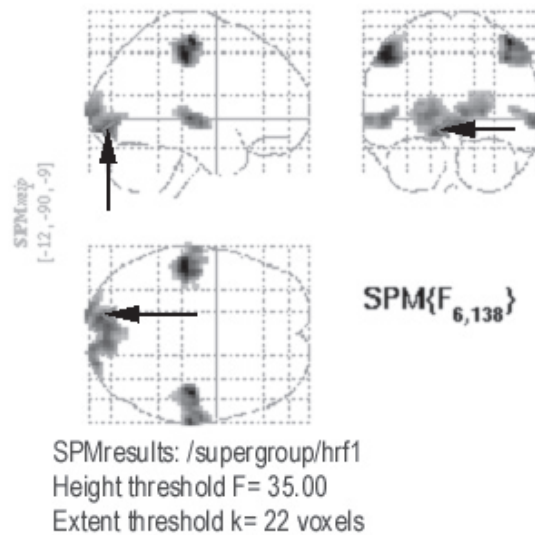


Figure 1: Glassbrain image showing the 6 major regions of activation. Red arrow points to the peak activation in the left visual cortex, which occurs at coordinates (-12, -90, -9).

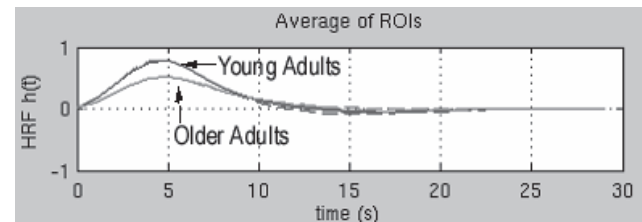
After the timecourses were extracted, the individual HRFs for each ROI were estimated using first- and second-order functions with a program that performed Fourier analysis. The functions were checked for relatively high fit correlations with the raw timecourse data (0.7 or above) for both first- and second-order fits. After saving the data, a Matlab-based custom program was used to combine the timecourses for the young and old participants so that the results could be compared and analyzed to discover the differences in the HRFs due to age.

Next, instead of analyzing the expected regions of interest, the timecourses for only the peak voxels from each participant's six ROIs were extracted. These six voxels were located in the left and right motor, auditory, and visual regions of the brain. Due to individual differences, some adults might not show as much activation in expected regions of interests but still have the same amount of peak activation, thus the peak voxels were examined in addition to the ROIs. The HRFs for each voxel of interest (VOI) were estimated and the graphs were checked for high correlation (>0.7) with the raw data for both first- and second-order fits. Then, the graphs for each VOI of the young and old adults were combined to compare the results of the two groups.

Statistical comparisons were conducted at an alpha level of .05.

Results and Discussion

The data collected from this study showed very reliable results. The estimation of the HRFs for the ROIs using a second order function had an acceptable correlation with the raw data. The average fit correlations of the HRFs with the raw timecourse data for the two scan sessions were high for both groups (0.90 for the younger adults and 0.82 for the older adults). However, the older adults had a lower correlation, indicating that their raw timecourse data was more irregular than that of the younger participants. The variability in this



group could be due to the fact that aging might have different effects on different adults, with some older adults having less cognitive decay than others. Some older participants might also have health problems affecting their hemodynamic responses. Since younger participants were experiencing

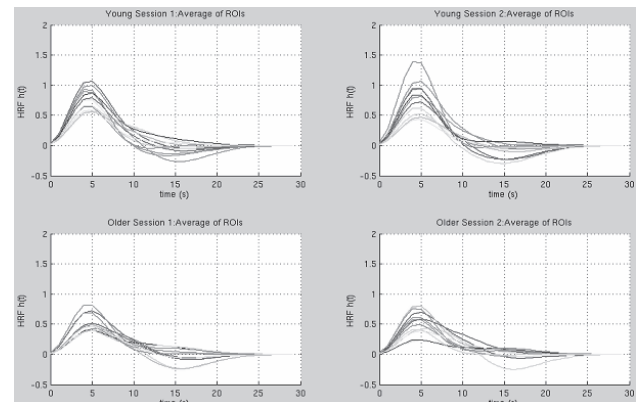


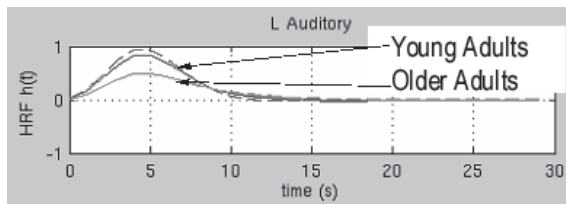
Figure 3: Individual differences in HRFs within each group for scan 1 and 2

fewer effects due to aging or pathological reasons, their hemodynamic responses were more consistent. Nonetheless, the fitted HRFs were generally accurate in predicting the neuronal responses for the two groups.

For the HRFs estimated from group-specified ROIs, the mean individual test-retest correlation between the two scan sessions was 0.98 for the young participants and 0.96 for the old. For the raw data, the mean individual test-retest correlation was 0.81 for the young and 0.73 for the old. The raw data showed some discrepancy across the two scan sessions, but nonetheless still displayed very high correlations, indicating that the data collected from this study was consistent for the two scan sessions and thus reliable. In comparison, the HRFs improved upon the correlations from the raw data and appeared to provide a more reliable measure of the hemodynamic responses of the two groups.

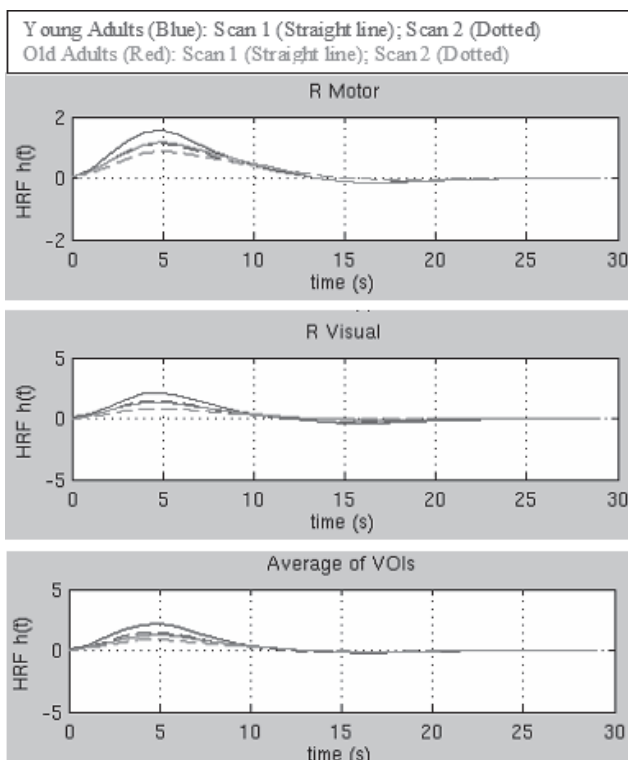
The correlations between the HRFs for the regions of activation and the canonical were also very good, averaging 0.94 for the young adults and 0.91 for the older adults. Since they were similar and high for the two participating groups, the canonical HRF is a good predictor of the HRFs in the different regions, thus implying that the canonical is useful in research such as adult developmental studies. In addition, the correlations between the HRFs for the different regions of activation were also good, averaging about 0.97 for the young participants and 0.93 for the old. This showed that the neuronal response is similar in different parts of the brain.

All the HRFs exhibited a similar bell-shaped curve that first rises to the peak activation and then slowly dips down and levels off to equilibrium. This was consistent between the old and young adults and also across different brain regions.



The similarity in the HRF shape showed that the human hemodynamic response follows a similar trend.

There were individual differences across both groups in peak activation and length of activation. The range in peak amplitude for the first scan was about 0.5 for the young adults and 0.6 for the old adults. The range for the second scan was around 1.0 for the young and 0.6 for the old. In addition, some participants in both groups reached equilibrium sooner than others. Some also had a small dip in activation after approaching their equilibrium state.



ROI- Peak Amplitudes

Young Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	0.616	0.614	0.874	0.743	0.826	1.03	0.793
Scan 2	0.629	0.622	0.958	0.779	0.799	0.971	0.793
Old Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	0.437	0.430	0.497	0.492	0.577	0.655	0.521
Scan 2	0.452	0.422	0.497	0.482	0.574	0.641	0.520

ROI- Time to Peak (seconds)

Young Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	5.50	5.83	5.58	5.50	5.83	5.83	5.75
Scan 2	5.58	5.67	5.50	5.25	5.75	5.83	5.83
Old Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	6.00	6.33	6.00	6.67	5.75	5.92	6.00
Scan 2	6.25	5.92	5.83	6.50	5.83	5.83	5.92

VOI- Peak Amplitudes

Young Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	1.53	1.56	2.89	2.73	2.68	2.08	2.18
Scan 2	1.20	1.22	1.66	1.84	1.73	1.50	1.48
Old Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	1.13	1.17	1.23	1.28	1.46	1.34	1.24
Scan 2	0.954	0.918	0.914	0.879	0.941	0.840	0.886

VOI- Time to Peak (seconds)

Young Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	6.25	6.00	5.75	5.58	5.92	5.92	5.92
Scan 2	6.17	6.17	5.58	5.50	5.83	6.00	5.83
Old Adults							
	Left Motor	Right Motor	Left	Right	Left Visual	Right	
Scan 1	6.33	6.33	5.75	5.83	5.92	5.92	5.92
Scan 2	6.33	6.50	5.83	7.83	5.92	6.17	5.92

Despite the similarity in shape and the individual differences in HRFs within each group, the old and young adults differed in the time to reach peak activation and in the amount and length of activation. In the estimation of the individual HRFs for the ROIs, the older participants took a longer time to reach peak activation, averaging about 6.00 seconds for scan one and 5.92 seconds for scan two, while the young adults took 5.75 seconds for the first scan and 5.83 seconds for the second, although these differences were not statistically significant. The older participants also had a lower peak of activation, indicating that their response to the stimuli was not as high. The average peak amplitude for both scans was 0.52 for the old and 0.78 for the young, which was a significant difference, $t(22) = 3.44$, $p = .002$. In the left auditory cortex, the younger adults had about two times more peak activation than the older adults. The younger adults also reached equilibrium sooner, indicating that their length of activation was shorter. The length of activation was around 11 seconds for the younger adults and 15 seconds for the older adults. This was consistent for both scan sessions.

However, the data collected from the peak voxels within each ROI implied that aging has less influence on hemodynamic responses. The time to reach peak activation was similar and the peak amplitude was also very close for the two groups. For example, in the right motor and visual VOIs for the two groups, the older adult HRFs were very similar to those of the younger participants. The peak activation for older adults in the first scan session (1.24) was close to the peak activation for younger adults in the second scan session (1.48). This could be due to sensory adaptation since the younger participants might have adapted to the stimuli and responded less to them during the second scan. However, the older participants also showed this adaptation since their second scan peak activation was lower than their first scan. Therefore, one can still conclude that aging lowers the amount of activation and increases the length of activation.

Conclusion

This study confirmed the findings of several other similar studies by showing that aging affects indirect measurements of neuronal response. Younger adults in this study had a higher peak of activation and reached peak activation and equilibrium sooner when presented with visual, auditory, and motor stimuli. Older adults had a lower and longer response, suggesting that their mental responsiveness was reduced relative to those of their younger counterparts. However, as discussed in the introduction of this paper, pathological influences related to aging can also affect one's neuronal response. Although the participants in this study were all healthy adults, the older adults might have experienced more small "strokes" or other health issues throughout their lives that reduced the rate of rise and peak hemodynamic responses.



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