# Age-related Increases in spatial variability of fMRI-BOLD activation is neural or vascular in origin

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**Introduction:** Normal aging is associated with changes in the cerebrovascular function, neuronal structure and cellular metabolism. As a person ages, dramatic neural plasticity occurs leading to differences in the amplitude and spatial extent of task-induced functional Magnetic Resonance Imaging (fMRI) responses and presents challenges of estimating altered activation due to disease [1]. It is hence necessary to delineate the neural and vascular differences in the fMRI signal in normal aging prior to interpreting results regarding neural plasticity in aging. In this study we investigate the neural and vascular origins of the BOLD signal response variability in young and aged humans.

**Methods:** Twelve younger healthy human subjects (6M and 6F; mean age: 24 years; range: 19-27 years) and twelve older healthy subjects (5M and 7F; mean age: 58 years; range: 55-71 years) with no history of head trauma and neurological disease were scanned in a 3T PHILIPS MR-scanner. The Institutional Review Board of the University of Texas at Dallas approved all experimental procedures. Each subject performed a breath hold (BH), bilateral fingertapping (FTAP) or Digit-Symbol Substitution task (DSST) paradigm. High-resolution T1 weighted anatomical images were obtained from all subjects. Gradient echo-EPI images were subsequently obtained during rest, BH, FTAP and the DSST task. 32 slices were obtained in the axial plane covering the entire brain. Imaging parameters were: FOV of 22 cm, matrix size of 64x64, TR/TE = 2000/30 msec and slice thickness of 4mm. 110 EPI images were obtained during each of rest, BH, DSST and FTAP tasks. To determine activated areas during FTAP, a voxel-wise cross-correlation of the BOLD signal time course was performed with the boxcar reference function representing the FTAP task. Activation maps were determined using a threshold of 0.35 for the correlation coefficient (Bonferroni corrected $p<0.003$; Bandettini et al., 1993). During BH, the boxcar reference function was appropriately shifted to take into account the large hemodynamic delay during the BH response. BH-activation maps were determined using a threshold of 0.30 for the correlation coefficient (Bonferroni corrected $p<0.005$). To determine activated areas during the DSST task, a gamma-variate function was convolved with the task reference function and cross correlated with the BOLD signal on a voxel-wise basis. DSST-activation maps were determined using a threshold of 0.20 for the correlation coefficient.

**Fig 1**

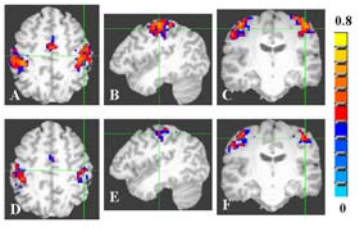



**Fig 2**

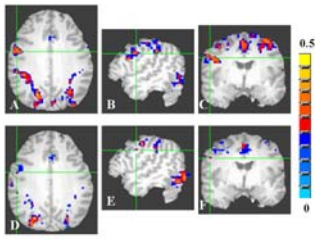
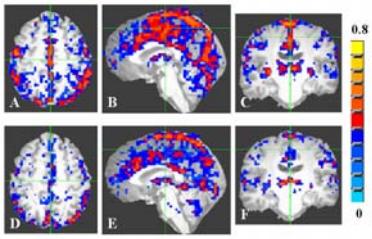



**Fig 3**




**Results and Discussion** Fig 1A-C shows the activation during the motor task in the younger and Fig 1D-F in the older group. The DSST task activated several brain regions including the Broadman areas 7, 9, 18, 19, 24, 31, 40, 44 and 46 in both young and old subjects. Fig 2A-C shows the activation during the DSST task in Broadman area-9 in the young and Fig 2D-F in the older group. Fig 3A-C shows the BH-induced activation in young while Fig3D-F shows the activation in the old. As observed from Figs 1, 2 and 3, the spatial extent of the group activation maps was significantly smaller in the older subject group when compared to the younger during all tasks. Fig 4 shows the spatial extent of activation during the motor, cognitive and the breath hold task and the reduction in the spatial overlap of activation as the number of subjects increased in each group. The spatial extent of activation was relatively larger in the older subjects compared to the younger when overlap between any one subject's activation was considered (Fig 4A1 and B1). In other words, the older subjects displayed a relatively larger spatial variation in the motor task-induced response when compared to the younger which also resulted in a faster disappearance of the spatial overlap of activation with increasing number of subjects in the old group (Fig 4B1-B7 and G) when compared to young (Fig 4A1-A7 and G). A similar trend was observed during the cognitive (Fig 4C1-C5 and H for young) and (Fig 4D1-D5 and H for old) and BH tasks (Fig 4E1-E5 and I for young) and (Fig 4F1-F5 and I for old).

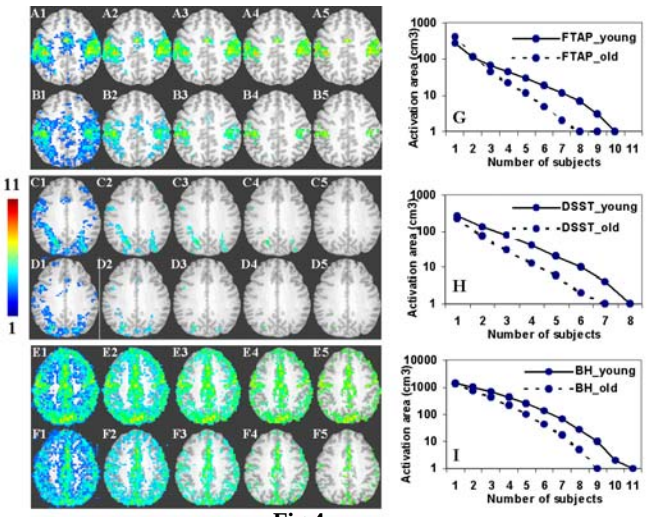



**Fig 4**

**Table 1:** Activation area (in $cm^3$) in response to the motor (FTAP), cognitive (DSST) and hypercapnia (BH) tasks in young and old subjects.

| Subject | young | | | old | | |
|---|---|---|---|---|---|---|
| | FTAP | DSST | BH | FTAP | DSST | BH |
| 1 | 91.71 | 87.20 | 577.56 | ---- | ---- | ---- |
| 2 | 61.10 | 57.30 | 1005.47 | 78.40 | 19.18 | 975.32 |
| 3 | 65.85 | 70.54 | 1019.43 | 22.28 | 40.29 | 382.81 |
| 4 | 258.56 | 75.06 | 977.85 | 47.91 | 57.06 | 452.89 |
| 5 | 83.27 | 87.85 | 526.42 | 53.72 | 65.97 | 813.12 |
| 6 | 113.82 | 129.83 | 974.92 | 346.69 | 32.02 | 407.97 |
| 7 | 87.61 | 50.96 | 792.37 | 71.31 | 33.01 | 652.86 |
| 8 | 61.57 | 75.77 | 300.19 | 169.88 | 62.69 | 266.35 |
| 9 | 68.67 | 57.41 | 391.20 | 251.16 | 58.17 | 643.47 |
| 10 | 109.84 | 42.28 | 491.47 | 70.43 | 73.42 | 575.68 |
| 11 | 123.56 | 120.33 | 659.25 | 42.28 | 131.47 | 473.71 |
| 12 | 68.26 | 101.10 | 336.54 | 196.98 | 68.08 | 647.99 |
| **Mean** | **99.49** | **79.64** | **671.06** | **122.82** | **58.31*** | **572.02** |
| **SD** | **54.46** | **27.12** | **273.72** | **104.24** | **29.91** | **204.50** |
| **CV** | **0.55** | **0.34** | **0.41** | **0.85** | **0.51** | **0.36** |

* $P<0.05$ compared to DSST in young subjects; unpaired t-test

Subject-wise activation area for all the three tasks is shown in Table 1. No significant difference was observed in the mean activation area between the young and old groups during the motor task (Table 1). However, the activation area during the cognitive task was significantly lesser in the older subject group when compared to the younger (Table 1). Inter-subject variability in the activation area was assessed through the coefficient of variation (ratio of standard deviation and mean). Inter-subject variability in activation area during the motor or cognitive task was higher in the older subject group when compared to the younger. No significant difference in the mean activation area was observed between the younger and older groups during BH. However, a comparable inter-subject variation in the BH activation area was also observed between the younger and older groups (Table 1). The decrease in average area of activation during the motor, cognitive or the BH task in the elderly was mainly due to a relatively larger spatial variability in activation. In addition to spatial variability, the decrease in the average area of activation during the cognitive task in the elderly was also due to a significantly lesser area of activation in the older subjects.

**Conclusion:** The larger spatial variability in activation in the elderly over the motor, cognitive and BH tasks suggests that normal aging may spatially rearrange brain function in a subtle manner depending on existing areas of efficient cerebrovascular function.

**References:** [1] D'Esposito M, Deouell LY, Gazzaley A. Nature Reviews Neuroscience 2003; 4: 863–872.