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Comparability of Functional MRI Response in Young and Old during Inhibition

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Abstract

An important issue in examining special populations with fMRI is the integrity of the hemodynamic response. Although the application of fMRI to aging issues is growing rapidly, very little systematic study of the hemodynamic response has been done in older individuals and no studies have examined it using cognitive rather than perceptual or motor tasks. As such, fMRI was employed with 28 healthy young and older adults on an inhibitory control task. The results showed that although older and young adults differed in task performance and activation patterns, they had comparable hemodynamic responses. The results suggest that activation patterns during inhibition, which predominantly showed increased activation in elders, were not due to vascular confounds or specific changes in hemodynamic coupling.

Keywords: event-related fMRI, inhibition, aging, hemodynamic coupling, recruitment, cognition.

Introduction

Cognitive neuroscience research, which focuses on revealing brain-behavior relationships, is most recently being applied toward understanding age-related declines in cognitive abilities such as memory and attention. The extant neuroimaging literature on cognitive aging thus far is small but growing rapidly. Indeed, although there are some inconsistencies, a common finding is that older adults activate more regions of the brain during tasks than do young adults, a finding that is often called "recruitment" [1-5].

One drawback, however, to the use of fMRI to study aging-related cognitive issues is that because the underlying physiological principle on which fMRI is based is hemodynamic coupling to neuronal activity [6], generalized cerebrovascular changes associated with aging could alter one or more parameters of the hemodynamic response. Indeed, studies evaluating visual cortex response to passive stimulation reported decreased fMRI signal amplitude in older adults [7,8], which was suggested could be due to an age-related alteration in functional activity or hemodynamic coupling [8]. Motor cortex response to a 10 s hand squeezing task also showed altered rise but not fall time in elders, suggesting slowed signal due to vascular changes [9]. These findings are particularly important in light of other reports that older adults have somewhat noisier signals (i.e., greater variability) than young adults, which could confound interpretation whenever elders exhibit reduced activation relative to young [7,10]. Importantly, purely sensory or motor tasks, for which older adults have less acuity and ability [11] could reduce detectable signal magnitude, which could be exacerbated by increased variability in the signals of older participants [12-14]. Without some correction for differential

"performance" in the groups, the meaningfulness of the result is unclear and the issue of hemodynamic integrity remains unresolved. A sensory-motor response task recently showed marked amplitude reductions in elders in visual cortex, but comparable signals to young in other regions and when overall relative activation changes were measured [15]. However, no studies have examined whether there are age-related differences in hemodynamic response properties during cognitive tasks or under comparable performance conditions.

We therefore used event-related fMRI to evaluate hemodynamic response parameters in 28 healthy participants, 14 older and 14 young adults during an inhibition (go/no-go) task. The data are a subset of those used in a previous study [5]. Only accurately performed trials were included for analysis, essentially equating the participant groups for task performance. Each response parameter was computed for all active brain voxels of successful trials for each participant and then averaged across the clusters of interest. Healthy older and young adults were expected to exhibit comparable hemodynamic response parameters.

Materials and Methods

Participants. Fourteen young adults (8 M, 6 F) aged 19 to 44 (mean = 29.7; SD = 8.3) and fourteen older adults (6 M, 8 F) age 60 to 77 (mean = 71.1; SD = 4.3) participated in the study. All older adults had Mini-Mental State Exam [16] scores above 26 (mean = 28.6, SD = 1.5) and Geriatric Depression Scale [17] scores below 10 (mean = 2.5, SD = 2.3). All participants were right-handed, highly educated (young = 15.7 years, SD = 1.6; old = 18.2 years, SD = 2.0), and free of medications and major medical, neurological, and psychological problems at the

time of testing. The Internal Review Board approved all procedures and written informed consent was obtained prior to testing.

Task. The go/no-go inhibition task is described in detail elsewhere [5,18]. It presented a serial stream of letters, one each 500 ms with a 0 ms interstimulus interval, with intermittent semi-random targets requiring response (average every 3.5 sec; 150 total) and lures (response to be inhibited) quasi-randomly and rarely (>15 second inter-lure interval; 25 total).

Neuroimaging. Whole-brain fMRI imaging was conducted on a 1.5T GE Signa scanner with a 30.5 cm i.d. 3-axis local gradient coil and an endcapped quadrature birdcage radio-frequency head-coil [19], 7mm contiguous sagittal slices, a blipped gradient echo-planar pulse sequence (TE = 40 msec; TR = 2000 msec; FOV = 24 cm; 64 x 64 matrix; 3.75 mm x 3.75 mm in-plane resolution), and spoiled GRASS anatomic images for anatomical localization [20]. Analysis was performed with AFNI v. 2.2 [21]. Functional images were modelled with a γ-variate function using non-linear regression (NLR) optimization[5,18]. The model, $y = kt^r e^{-t/b}$, allowed the scaling parameter, *k*, to vary freely, constrained onset time (*t or t0*) to within 4 sec of lure events, and constrained the exponential parameters, *r* (largely representing rise time) and *b* (largely representing fall time), to a range similar to previously published estimate [22]: $8 \leq r \leq 9$, $0.15 \leq b \leq 0.45$. Parameters and derived quantities, such as response magnitude, computed as % area under the curve (AUC), were smoothed (4.2 mm full-width-at-half-maximum isotropic Gaussian filter) and stereotaxically normalized prior to group analyses. Separate, voxel-wise, one-sample *t*-tests were then performed for old and young groups against the null hypothesis, using % AUC and a cluster criterion of 100 mm^3 of

contiguous, significant voxels. A Monte-Carlo randomization procedure established a false-positive statistical threshold for clusters or regions of interest (ROIs), accounting for multiple comparisons ($t = 4.22$; $p < .001$) [5]. These clusters were then combined and compared between groups by t-test ($p < .01$ criterion) [5].

Hemodynamic parameter analysis. The four parameters (*t0, k, r, b*) were each averaged across all voxels of each significant cluster for each subject, followed by *t*-tests between groups for each averaged cluster parameter value ($p < .01$ criterion). The large number of comparisons increased the false positive likelihood, but this risk was deemed acceptable because of the hypothesis of no differences. A second analysis with less Type I error risk, averaging the parameters across the ten largest clusters, was also used.

Results

Behavioral data. Overall, participants in both groups performed well on the task (O = 98.1% (SD = 1.2), Y = 99.1% (SD = 1.7), $t(26) = 1.8$, $p > .05$). However, older adults were slower to respond to targets (O = 505.4 ms (SD = 58.6), Y = 459.6 ms (SD = 46.0), $t(26) = -2.3$, $p < .03$) and had fewer “successful inhibitions” (O = 79.1% (SD = 14.8), Y = 92.6% (SD = 4.1), $t(26) = 3.3$, $p < .01$) than young adults. This finding is consistent with the larger data set from which the current data were taken [5].

fMRI data. The activated clusters and their group differences are presented in Table 1. There were no significant group differences in right prefrontal clusters, but several left hemisphere clusters, particularly in the prefrontal cortex, were significantly more active in older participants, a finding consistent with that found

with the larger dataset already published [5]. Young adults demonstrated greater activation than older adults only in two clusters: right postcentral gyrus and left fusiform gyrus.

The hemodynamic response parameter averages for each cluster by group are listed in Table 1. Significant between-groups differences in hemodynamic response parameters were infrequent and limited to the domain of magnitude with the exception of three clusters. The differences with respect to magnitude were consistent with the %AUC analysis results. Figure 1 depicts modeled response curves in the three largest clusters: right parietal, right middle frontal, and left inferior frontal areas. Clusters in left and right thalamus and one in left premotor area were different between groups in rise time, where older adults had faster (i.e., smaller) rise times than young adults.

INSERT TABLE 1 ABOUT HERE

INSERT FIGURE 1 ABOUT HERE

To examine the variability in the hemodynamic responses for lure trials between subjects rather than simply between groups, we calculated average waveforms for each subject with 95% confidence intervals calculated from the group SD for each parameter under both extremes (i.e., all high/early or low/late values). The result of this analysis using the ten largest clusters (using all clusters produced nearly identical results) is shown in Figure 2, which shows that older and younger participants had comparable averages and comparable variability of responses. However, the high confidence interval shows the possibility of slightly earlier and larger waveforms for the older adults.

INSERT FIGURE 2 ABOUT HERE

Discussion

The purpose of this study was to examine the integrity of the hemodynamic response in older adults as compared to young adults on an inhibition task. Analysis of the hemodynamic response parameters revealed no significant between-groups differences in onset, rise or fall parameters for any of the activated regions, except in two thalamic clusters and one premotor cluster for rise, which had a smaller (i.e., earlier) rise for older subjects. In addition, the cluster-averaged waveform (Figure 2) suggested that older and younger averages and variability were comparable, with the exception of slightly earlier and more robust *k* parameter at the high end for older participants. This latter finding could be due to somewhat more extreme responses at the high end by older subjects. In contrast it could simply be due to the larger number and size of the clusters with greater magnitude of response produced by older participants. Overall the averages and variability were quite comparable and well within expected ranges for normal hemodynamic responses. These findings support the hypothesis and are generally consistent with the findings of Buckner et al. [15] and D'Esposito et al. [10], suggesting that the group differences in activation were not due to age-induced hemodynamic factors. The present findings, in fact, call into question whether such changes occur in healthy aging. Indeed, the current results suggest that the hemodynamic differences previously reported [7-9] might have been exacerbated by group differences in sensory-motor acuity. Furthermore, the results clearly indicate that the parameters of the general hemodynamic model used to analyze these data sets are appropriate for and not violated by older subjects. Indeed, the NLR

optimization procedure used arrives at the best-fitting function for each voxel time series, while also allowing significant variability within the data and maintaining a hemodynamic waveform, which appears optimal for comparing groups expected to differ on behavioral or functional dimensions, such as old and young. Finally, because young adults exhibited some degree of activation in many of the same left prefrontal regions that were significantly more activated by older adults (Figure 1), the results suggest that left prefrontal regions may be available to participate in inhibition, when or if needed, with those on the right [23].

Conclusion

In sum, elders, as compared with young adults, had comparable hemodynamic response properties, increased magnitude of activation, and a more bilateral activation pattern for an inhibition task. The results suggested that age-related difficulty with inhibition is not associated with changes in response functions or hemodynamic coupling. Furthermore, evaluations of healthy older and young subjects in interaction with various cognitive task conditions would not be generally confounded by alterations in hemodynamic properties.

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Table 1. Clusters of statistically significant ($p < .001$) contiguous activation associated with response inhibition in either the young or older group shown with group differences and average hemodynamic response parameters.

		Vol				Young:					Older:			
Side/	**Lobe - BA**	**(μl)**	**X**	**Y**	**Z**	***t***	**r**	**b**	**t0**	**k**	**r**	**b**	**t0**	**k**
Right	Frontal- 10	460	39	51	1	-2.6	6.82	.156	.752	298.7	5.66	.151	.630	650.6
	10/46	206	42	40	-1	1.0	7.69	.198	.825	717.2	7.93	.197	.838	350.5
	8/9/46	3664	37	26	31	.96	8.09	.186	.955	752.7	7.99	.187	.918	579.9
	6	725	30	-5	57	-1.3	8.27	.192	.953	246.3	7.98	.188	.868	668.4
	6	353	32	4	38	.30	8.39	.191	.932	533.8	8.33	.188	.882	569.9
	10	103	22	52	19	-1.5	8.29	.192	1.03	611.0	7.49	.191	.918	602.2
	6	335	30	15	52	-1.4	7.85	.186	.900	440.5	7.39	.181	.892	412.5
	6	136	50	1	32	-1.5	8.23	.189	.922	287.2	8.31	.190	.963	803.9
	13	1524	39	14	3	1.5	8.04	.19	.917	856.6	8.23	.191	.843	573.3
	Parietal- 40/7	4597	42	-51	41	-.15	7.91	.186	.917	611.5	7.82	.185	.852	618.1
	31/7	438	1	-54	33	-3.3*****	8.43	.195	.921	-127.1*****	8.33	.191	.940	660.7*****
	19	301	41	-69	39	-1.8	6.57	.150	.753	96.9	5.73	.146	.626	711.2
	5	142	55	-13	23	2.8*****	8.06	.186	.992	556.2	8.38	.190	1.01	406.9
	Occipital- 18	646	39	-77	0	1.5	7.61	.179	.952	571.6	7.28	.166	.753	430.7
	Temporal- 19	106	40	-68	-13	-.48	8.11	.190	.894	314.8	6.37	.160	.803	659.1
	22/39	517	44	-42	3	-2.0	8.38	.193	1.03	280.4	8.32	.188	1.01	483.7
	DMT	470	8	-16	8	-3.6†	8.42*****	.197	.959	321.9*****	8.29*****	.198	.877	920.0*****
	VAT	145	11	-6	7	.34	8.37	.193	1.01	453.2	8.35	.189	.949	444.5

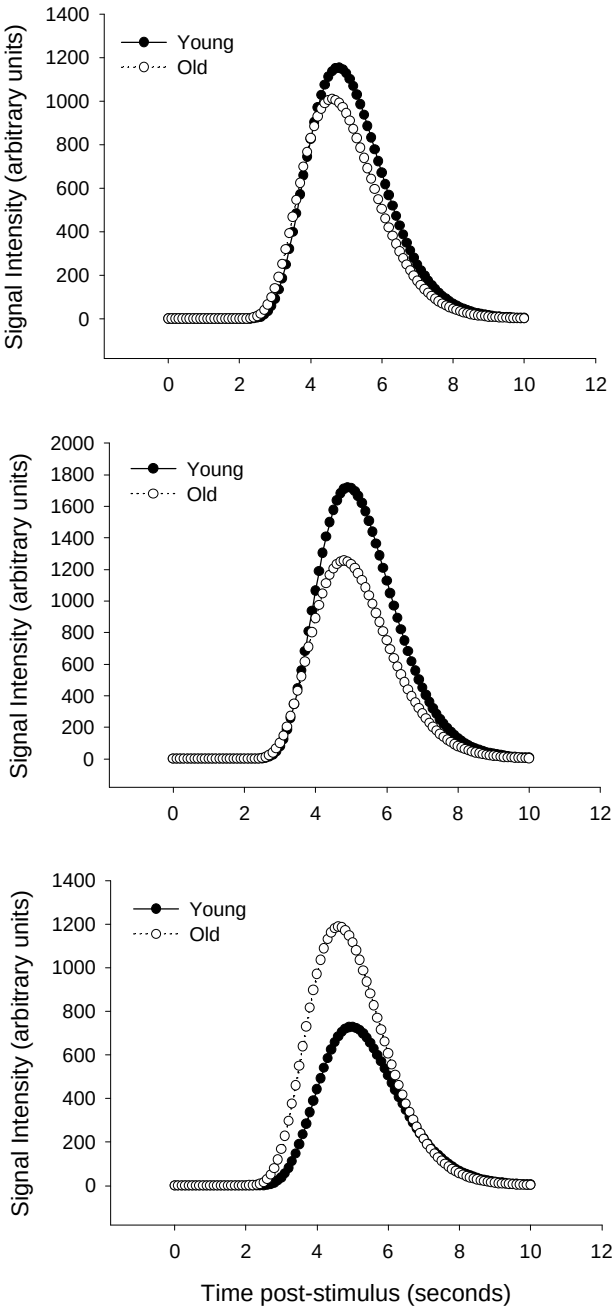
Left/ Frontal-44/6/4/6/9	5073	-43	9	31	-6.1†	8.18	.191	.923	233.6	7.92	.186	.837	635.0
6	206	-4	-6	49	-1.9	8.40	.178	1.01	42.7	8.36	.186	.889	449.7
6	359	-33	-1	55	-1.4	8.23	.191	1.05	403.9	7.45	.187	.881	543.4
6/4	1135	-16	-2	58	-2.1	8.38	.195	1.01	189.1	8.29	.192	.93	484.1
6	136	-28	-15	59	-2.1	8.37	.196	.978	48.6	8.29	.192	1.03	305.0
6	325	-7	16	62	-5.3†	8.04*****	.191	.960	-314.2*****	5.95*****	.164	.738	470.4*****
6	112	-5	28	55	-2.5	8.29	.196	1.01	257.8	6.33	.171	.717	474.5
4	157	-17	-26	58	-3.1*****	8.38	.193	.986	-251.3†	8.32	.189	.910	519.1†
13	241	-32	12	8	-2.4	8.37	.194	.984	224.3	8.32	.188	.875	749.0
Limbic- 32	1458	-1	17	42	-.05	8.37	.195	.973	672.0	8.34	.195	.857	585.8
Parietal- 19	261	-25	-67	35	1.2	8.39	.197	.990	207.4	8.32	.196	.988	548.3
40	3189	-42	-53	37	-2.3	8.24	.190	.917	307.3	8.01	.188	.918	627.8
Occipital- 18	108	-40	-82	-10	2.4	8.16	.194	1.01	365.0	6.21	.138	.704	447.1
Temporal- 19	320	-43	-62	-13	2.9*****	8.37	.199	1.04	573.5	7.01	.151	.715	369.8
21	303	-54	-28	-7	-2.3	8.06	.187	.903	258.3	7.98	.151	.860	899.9
VAT/DMT	453	-12	-10	11	-2.9*****	8.40*****	.201	.977	65.0*****	8.29*****	.171	.866	772.2*****

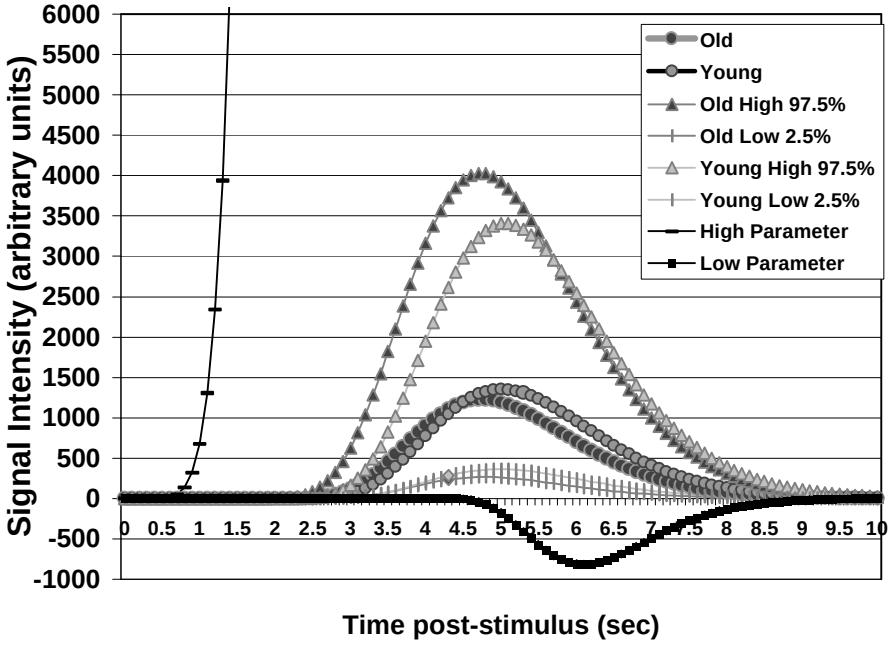
*****p < .01; † p< .001. BA = Brodmann area; DMT = dorsomedial thalamus; VAT = ventral anterior thalamus; r = rise time; b = fall time; t0 = onset time; k = magnitude. Coordinates are in mm from the anterior commissure [20] with positive is right (X), anterior (Y), and superior (Z). Negative direction of *t*-value indicates older group had greater activation than young group.

Figure Legends

Figure 1. Models of hemodynamic response during successful inhibitions (lures; “No-go”) for both young and older adults in the three largest activation clusters: right inferior parietal lobule (**a**), right middle frontal gyrus (**b**) and left inferior/middle frontal gyrus (**c**). The plotted symbols are for visual distinction only and do not represent actual datapoints. The groups did not significantly differ on any parameter in these clusters except in magnitude for **c** (old > young, $p \leq .01$). Overall the response parameters were predominantly comparable (see Table 1).

Figure 2. Models of hemodynamic response during successful inhibitions averaged across the ten largest clusters, separately for older and younger participants, including confidence intervals and high and low parameters. The plotted symbols are for visual distinction only and do not represent actual datapoints. The averages were comparable between groups.


Young
Old
Signal Intensity (arbitrary units)
Time post-stimulus (seconds)


Signal Intensity (arbitrary units)
6000
5500
5000
4500
4000
3500
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2500
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0
-500
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0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10
Time post-stimulus (sec)
Old
Young
Old High 97.5%
Old Low 2.5%
Young High 97.5%
Young Low 2.5%
High Parameter
Low Parameter