10-1-2003

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Accepted version. *NeuroImage*, Vol. 20, No. 2 (October 2003): 1384-1392. DOI.

Frontal Recruitment During Response Inhibition In Older Adults Replicated with fMRI

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Abstract: Recent research has explored age-related differences in multiple areas of cognitive functioning using fMRI, PET, and SPECT. However, because these studies used different tasks, subjects, and methods, little is known about whether the results of these studies are generalizable or repeatable. The present study replicated a previous study [Psychol. Aging 17 (2002) 56]

NeuroImage, Vol 20, No. 2 (October 2003): pg. 1384-1392. DOI.

using the same Go/No-go task with a subset of 11 of the original older adult subjects, and using the same fMRI scanner and imaging methods. A direct comparison was made between these participants at Time 1 and Time 2 for both behavioral and functional data. These participants were also compared to a new young adult group of 11 participants. Although the current young adult group did not perform as well as the original young adult group, the original finding of enhanced left prefrontal activation in older adults relative to younger adults was replicated. Furthermore, when comparing Time 1 to Time 2, older adults exhibited comparable areas of activation, but significantly greater magnitude of activation at Time 1 in a few clusters. The findings indicate that older adults exhibit more bilateral brain activity during this task than young adults, which appears compensatory and is repeatable over time. The magnitude of regional activation, however, may vary with extraneuronal factors such as signal-to-noise ratio or task experience. This study adds to existing research suggesting that bilateral frontal activation is a predominant finding in the aging literature, and not specific to certain tasks in age group comparisons.

Keywords: Aging, Prefrontal cortex, Neuroimaging, Inhibitory control, Executive function, Cognition

Introduction

As the neurophysiological and neuroanatomical underpinnings of cognitive changes with aging have become a more central area of research, the study of cognitive decline in older adults is being studied using newer techniques such as PET and fMRI, which have begun to point to some key findings. More specifically, although the nature of the tasks used to study age-related changes in cognition and neurophysiology within imaging paradigms have varied from facial recognition to verbal working memory, some task nonspecific findings have begun to emerge. Older participants exhibit extraneous areas of activation and greater bilateral activation in functional homologues (i.e., analogous brain regions in the contralateral hemisphere) where younger adults exhibited asymmetrical activation (Cabeza, 2002; Cabeza et al., 1997b; Grady et al., 1994; Madden et al., 1997, 1999; Nielson et al., 2002; Schachter et al., 1996, but see Grady et al., 1995; Jonides et al., 2000; Rypma and D'Esposito, 2000). A number of the imaging studies also report differences between younger and older adults in the inferior parietal lobule and the dorsomedial nucleus of the thalamus (DiGirolamo et al., 2001; Grady et al., 1994, 1995; Grossman et al., 2001; Madden et al., 1997, 1999; Nielson et al., 2002).

Based upon these findings, it has been suggested that perhaps the working memory, secondary memory, and inhibitory control deficits of older adults may be the result of changes within the frontal lobes (Nielson et al., 2002). Yet, it still remains unclear if these "parallels" in activation differences across studies are replicable in the standard methodological sense. Of crucial concern toward understanding the implications of functional neuroimaging research with aging is whether there are any parallels or consistencies between behavioral and functional findings that are comparable using similar methodologies, in addition to the existing findings reported above with different tasks and subjects. To date, no neuroimaging studies in aging have been replicated using the same participants and the same task (although see Grady, 2002, for three studies using similar face matching control tasks with different participants).

The present study was conducted as a replication of a recently published study (Nielson et al., 2002), where inhibitory control on behavioral measures in older adults was good but significantly worse than that of younger adults, and functional activity was equivalent across groups in areas typically associated with inhibitory control (e.g., right inferior frontal gyrus, right inferior parietal lobule; see Rubia et al., 2001, for a complete review), but also greater in older adults in left prefrontal areas. The findings supported a compensatory recruitment view of age-related differences (Cabeza, 2002; Madden et al., 1997). It was expected that the current study would replicate those findings. Specifically, it was predicted that older adults would perform less well than young adults and that young and older adults would have primarily comparable regions and magnitudes of activation, but with additional left prefrontal regions in older adults. Greater thalamic and left parietal activation in older adults was also expected based on the previous study. Furthermore, it was predicted that a direct comparison of repeated older adults' performances would produce comparable results from Time 1 to Time 2.

Materials and methods

Eleven healthy younger (4 males, 7 females; age: *M* = 28.09 years, SD = 4.11) and eleven healthy older participants (3 males, 8 females; age: *M* = 72.8 years, SD = 3.46) with comparable years of

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education (younger: *M* = 17 years, SD = 1.67, older: *M* = 18 years, SD = 2.32, *t* = −1.16, *P* = 0.26) gave signed informed consent as approved by Marquette University and the Medical College of Wisconsin. The older participants were a subset of those used in a previous study (Time 1; Nielson et al., 2002). The time elapsed between scanning sessions for older adults was an average of 14 months (*M* = 14.1 years, SD = 2.6, range 9–18). Normal cognitive and emotional status was verified in all participants by prescreening using an extensive phone interview, by additional screening at the time of the evaluation (Mini Mental State Exam, MMSE > 26, Folstein et al., 1975; Geriatric Depression Scale, GDS < 10, Sheikh and Yesavage, 1986; Snowdon and Hickie, 1987), and for older participants only, by a 3-h neuropsychological battery administered between Time 1 and Time 2. Two of 13 older participants collected during the study were excluded because of a mechanical failure in behavioral data collection, leaving the remaining 11 whose demographic and behavioral data are included herein.

The Go/No-go task, administered with Superlab Pro 2.0, is described in detail elsewhere (Garavan et al., 1999; Nielson et al., 2002). Briefly, participants were required to press a button on a keypad by responding to alternating target letters (e.g., *X, Y, X*) such that they were required to inhibit a response to a letter the second time it was presented without an intervening other target letter. Participants in the current study (Time 2 for older and younger subjects) completed this same task with a similar length and number of events, but the task was administered in two blocks of trials rather than four blocks used in the previous study (Time 1). This was done to minimize scanner time and the potential negative effects of undetected head movements between runs. This procedure yielded a slightly longer "active" total task time (Time 1 = 544", Time 2 = 572") but shorter total time (Time 1 = 1084", Time 2 = 752") because of waiting times between blocks. There were slightly different numbers of overall events for analysis than in the original study [Time 1 = 150 targets, 25 lures (6/1); Time 2 = 166 targets, 32 lures (5.19/1)]. A greater number of lures were included in the present study so that there would be more events for event-related analyses (see Bandettini and Wong, 1997) after removing errors. Functional data were collected in identical manners in all sessions.

A 1.5-T GE Signa scanner equipped with a 30.5-cm i.d. 3-axis local gradient coil and an endcapped quadrature birdcage radiofrequency head-coil was used for brain imaging (Wong et al., 1992). Nineteen contiguous sagittal slices 7 mm thick were acquired using a blipped gradient echo-planar pulse sequence (TE = 40 ms; TR = 2000 ms; FOV = 24 cm; 64 × 64 matrix; 3.75 × 3.75 mm in-plane resolution). High-resolution spoiled GRASS (1 × 1 × 1.1–1.3) anatomic images were acquired for later Talairach transformation (Talairach and Tournoux, 1988). Soft foam padding was used to limit head movements and earplugs were used for hearing protection. Prism glasses (with correction, as necessary) were used to view the task, which was back-projected on a screen at the participant's feet.

All data processing was conducted with the software package AFNI v2.2 (Cox, 1996). Algorithms used to detect and correct for three-dimensional motion and edge detection were applied to the functional echo-planar images after transformation from Fourier space. Then participants' functional images were viewed cinematically to detect uncorrected head movements. During this process, some signal abnormalities were noted in separate sagittal slices for one younger and one older participant, and these data were excluded from further analyses, yielding 10 participants in either group remaining for functional analyses.

Regression cannonicals were used separately for targets, lures (inhibitory trials), commission errors, omission errors, and missed opportunities, so that activation related to these wanted (inhibitory) and unwanted (all other cognitive/behavioral) events would not confound inhibitory-based activation or contribute to measurement error within the deconvolution procedure. Only activations for valid, correct inhibitory trials were averaged together to obtain a mean signal response for each voxel using a deconvolution procedure and an impulse response function was generated for inhibitory events. A nonlinear regression optimization procedure that is effective in separating signals that can be attributed to neural activity from noise in functional images in both healthy young (Ward et al., 1998) and healthy elders (Nielson et al., 2001) was used to model the averaged functional datasets with a gamma-variate function (Ward et al., 1998). Area under the curve (%AUC) for each voxel was expressed as a percentage of area under the hemodynamic response corrected by

baseline activation. These maps were converted to the standard stereotaxic coordinate system of Talairach and Tournoux (1988) after which a 4.2-mm full-width-at-half-maximum isotropic Gaussian filter was applied.

Between-subjects comparisons (older-young replication)

The data were converted to %AUC measures for voxels of interest for the younger adult group and then for the older adult group. The %AUC map for each group was then reduced to significant clusters for each group by using a combined threshold by cluster size method, (e.g., a cluster size of 109 mm^3 and threshold of 4.583). These group %AUC maps were then combined into an "overall" inhibition trial map (see Nielson et al., 2002, for a description of this procedure). Significant voxels were combined into contiguous clusters such that significant voxels and clusters closest to each other were included as one averaged %AUC cluster. This threshold was more stringent than in the prior study because there were fewer degrees of freedom (i.e., participants), while maintaining an identical Type I (false positive) error rate of 0.01.

Within-subjects comparisons (older adult retest, general repeatability comparison)

Functional activation maps were compared for older adults at Time 1 versus Time 2 using a paired *t* test after activation values for each person were transformed into *z* scores (relative to all %AUC values within the functional dataset corrected for each participant). This procedure is a standard method of normalization that allows for more direct comparisons of functional data across studies. Based on either significantly greater activation at Time 1 versus Time 2, or the reverse, clusters were extracted that surpassed the activation threshold of 4.78 and the cluster size threshold of 109 mm^3. The resulting clusters were used to extract average %AUC areas of activation for each person for each cluster. This analysis was used to look for any effects of Time that may be independent of those areas important for inhibitory control (see next paragraph).

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Within-subjects comparisons (older adult retest, inhibition-specific repeatability comparison)

Comparisons were also made for Time 1 versus Time 2 using a cluster extraction technique identical to that described above for the between groups analysis and in our prior work (Nielson et al., 2002) with combined cluster maps and extracted average %AUC values for each cluster. This analysis was based upon a two-step process whereby those areas most important for inhibitory control at each time period are derived first, followed by a comparison in activation of the combination of these two cluster maps. This technique is a more specific way of ascertaining potential differences between groups in areas important for inhibitory control. Again, these %AUC values were transformed into *z* scores in an identical fashion to that described above prior to computing *t* tests to make the data more directly comparable from Time 1 to Time 2.

Behavioral-activation relationships

To determine whether previously reported relationships between activation values and behavioral performance were repeatable over time, correlations of older adult's behavioral performance at Time 1 with normalized functional activation values at Time 1 were conducted. This procedure was repeated for Time 2. In other words, it was important to determine if there were behavior-activation relationships at Time 1 that were similar in magnitude, direction, and location to behavior-activation relationships at Time 2.

Results

Old-young replication

The behavioral data for the Go/No-go task are presented in Table 1. Results from independent samples *t* tests indicated that there was not a significant difference between younger and older adults in inhibitory control [percent correct inhibition (PCI), $t(9) = 0.20$, $P = 0.842$] or reaction time [$t(9) = -0.99$, $P = 0.335$], while older adults were significantly worse than younger adults in correct responses to targets [PCTR, $t(9) = 2.707$, $P = 0.03$]. Functional analyses between

younger and older adults derived 23 suprathreshold clusters for correct inhibitions. Average %AUC values for each cluster for each person were compared between groups and these results can be viewed in Table 2. Older adults exhibited greater activation in the inferior frontal gyrus (BA 9), the inferior parietal lobule (BA 40), the claustrum, and the putamen in the left hemisphere, and the medial (BA 6) and middle (BA 6) frontal gyri in the right hemisphere. No clusters were significantly more active for younger adults.

Table 1. Behavioral data for Time 1 and Time 2

	Older adults[a] (*N* = 11, Time 1 & Time 2) mean (±SD)	Young adults (*N* = 14, Time 1; *N* = 11 Time 2[a]) mean (±SD)	Old-young *t*	Old-young *P*
PCI Time 1	76.8 (20.8)	92.6 (4.2)	3.47	0.003
PCI Time 2	73.1 (13)	74.4 (14.6)	0.20	0.842[c]
t (*P*)	0.806 (.441)[b]	3.81 (.003)[c]		
PCTR Time 1	97.3 (2.2)	98.5 (2.6)	2.29	0.03
PCTR Time 2	87.7 (11.3)	97.9 (3.7)	2.707	0.03[c]
t (*P*)	−3.1 (.013)[b]	0.459 (.651)[b]		
RT targets Time 1	501.9 (71.2)	457.2 (46.9)	−2.8	0.009
RT targets Time 2	497.7 (70.2)	482.4 (62.5)	−0.99	0.335[c]
t (*P*)	0.523 (0.615)[b]	−1.11 (0.28)[c]		

[a]Time 1 and Time 2 reflect performances of the same participants in the Older adults column, but different participants in the Young adults column. PCI=percent correct inhibition; PCTR=percent correct target responses; RT targets=reaction time for correct responses to targets.
[b]Paired samples *t* test.
[c]Independent samples *t* test.

Table 2. Clusters of significant activation for younger and older adults at Time 2

Hem.	Lobe	Gyrus	BA	mm³	RL	AP	IS	*t*	*P*
Left	Frontal	Inferior frontal	9	549	−41	5	30	−5.01	0.001[c]
			9,10	469	−35	24	23	−1.75	0.100
		Middle frontal	9	511	−37	15	36	−3.18	0.005[b]
		Precentral	6	132	−41	−8	46	−2.06	0.062
	Parietal	Inferior parietal	40	325	−47	−56	39	−1.74	0.106
			40	151	−50	−34	23	−2.84	0.016[c]
		Supramarginal	40	116	−58	−48	30	−0.98	0.339
	Subcortical	Claustrum		187	−28	15	−1	−2.70	0.015[b]
		Putamen		396	−27	3	6	−3.16	0.005[b]
Right	Frontal	Medial frontal	6	149	8	−8	54	−1.91	0.072
			9	132	11	39	25	−3.33	0.004[b]

Hem.	Lobe	Gyrus	BA	mm³	RL	AP	IS	*t*	*P*
		Middle frontal	6	304	33	−13	39	−2.36	0.030[b]
			6	257	29	7	42	−2.00	0.060
			9	198	31	34	30	−0.26	0.798
			9	172	34	4	34	−1.61	0.125
			6	168	27	−7	53	−1.48	0.156
		Paracentral	4	304	12	−34	55	−2.03	0.058
	Limbic	Anterior cingulate	32	755	4	26	34	1.87	0.078
			32	533	10	9	47	−0.90	0.380
		Cingulate	23	194	8	−12	27	0.75	0.464
	Parietal	Postcentral	43	158	50	−14	18	−1.23	0.236
		Supramarginal	40	239	42	−51	31	−0.24	0.816
			40	146	54	−49	29	−0.02	0.986

[a]RL=left (−) to right (+) orientation in relation to midline; AP=anterior (+) to posterior (−) orientation in relation to the anterior commissure (AC); IS = inferior (−) to superior (+) in relation to the AC-PC line. Mean activation=0.021 %AUC for young adults and=0.041 %AUC for older adults.
[b]Significantly greater activation in older adults (negative *t* values) relative to younger adults, but both have positive %AUC.
[c]Significantly greater activation in older adults relative to younger adults, younger adults have negative %AUC.

Older adult retest

For older adults, there were no significant differences between Time 1 and Time 2 for PCI [$t(9) = 0.806$, $P = 0.441$] and reaction time [$t(9) = 0.523$, $P = 0.615$], but older adults had significantly lower PCTR at Time 2 compared to Time 1 [$t(9) = -3.1$, $P = 0.013$; see Table 1]. Functional data clusters associated with correct inhibitions that were significantly different from Time 1 to Time 2 were derived and the average %AUC values for each participant were individually normalized and compared using paired *t* tests. Of the six clusters extracted, all had greater normalized functional activation at Time 1 compared to Time 2. These six clusters, described in Table 3, were located in bilateral lateral and medial frontal lobes (BA 6 and 9) and left angular gyrus (BA 39).

Table 3. Significant clusters in direct retest Time 1 vs. Time 2[a]

Hem.	Lobe	Gyrus	BA	mm³	RL	AP	IS	*Z* Time 1	*Z* Time 2	*t*	*P*
Left	Frontal	Inferior frontal	9	248	−47	9	31	1.35	0.40	2.42	0.04
		Medial frontal	6	111	−11	0	58	1.26	0.60	2.39	0.04
		Middle frontal	6	118	−45	2	40	1.01	0.14	2.83	0.02
	Parietal	Angular	39	374	−33	−60	32	1.06	0.31	3.23	0.01

Hem.	Lobe	Gyrus	BA	mm³	RL	AP	IS	*Z* Time 1	*Z* Time 2	*t*	*P*
Right	Frontal	Medial frontal	6	123	8	−4	52	1.06	0.32	3.36	0.01
		Middle frontal	6	201	33	−4	55	0.83	0.22	4.04	0.00

[a]Hem.=Hemisphere; mm³=cluster volume in cubic millimeters; RL=left (−) to right (+) orientation in relation to midline; AP=anterior (+) to posterior (−) orientation in relation to the anterior commissure (AC); IS=inferior (−) to superior (+) in relation to the AC-PC line. All clusters had significantly greater normalized activation at Time 1 (positive *t* values) versus Time 2. *Z* scores reflect mean activation change for each group in that particular cluster. Mean *Z* scores for these clusters are Time 1=1.09 and Time 2 = 0.332.

Clusters were also generated comparing each time versus the null hypothesis, combining clusters across times, and extracting average activation for each person for each time (see Materials and methods). Paired *t* tests were computed between normalized activation values in each of 26 clusters at Time 1 and Time 2. These values are illustrated in Table 4. Of the 26 clusters, six were significantly greater at Time 1 versus Time 2: the left medial frontal gyrus (BA 6) and inferior parietal lobule (BA 40) on the left, and the inferior (BA 9), middle (BA 6), and superior (BA 10) frontal gyri, and precuneus (BA 7) on the right. One cluster in the right postcentral gyrus (BA 43) was greater at Time 2 versus Time 1. Nineteen clusters were not significantly different between Time 1 and Time 2.

Table 4. Combined clusters of significant activation for older adults at Time 1 and Time 2[a]

Hem.	Lobe	Gyrus/lobule	BA	mm³	RL	AP	IS	*Z* Time 1	*Z* Time 2	*t*	*P*
Left	Frontal	Inferior frontal	9	1002	−43	6	32	0.90	0.59	1.70	0.12
		Medial frontal	6	193	−10	0	58	0.80	0.24	2.31	0.05[b]
		Middle frontal	9	488	−37	15	35	0.44	0.60	−1.18	0.27
				453	−35	24	23	0.48	0.67	−0.64	0.54
		Precentral	6	121	−41	−8	46	0.39	0.37	0.12	0.91
	Limbic	Insula	13	481	−38	14	3	1.06	0.83	0.85	0.42
	Parietal	Inferior parietal	40	1587	−38	−57	35	1.15	0.39	3.72	0.01[b]
				148	−50	−34	23	0.31	0.41	−0.33	0.75
		Supramarginal	40	110	−58	−48	30	0.61	0.68	−0.16	0.88
	Subcortical	Putamen		388	−27	3	6	0.58	0.87	−1.12	0.29
Right	Frontal	Inferior frontal	9	145	45	3	33	0.89	0.20	2.87	0.02[b]
		Medial frontal	6	364	7	−5	53	0.75	0.40	2.13	0.06
			9	126	11	39	25	0.60	0.47	0.41	0.69
		Middle frontal	6	463	30	−5	54	0.76	0.30	4.35	0.00[b]

Hem.	Lobe	Gyrus/lobule	BA	mm³	RL	AP	IS	*Z* Time 1	*Z* Time 2	*t*	*P*
			6	255	29	7	42	0.58	0.67	−0.50	0.63
			10	170	36	38	10	1.05	0.50	1.42	0.19
			9	167	34	4	34	0.24	0.61	−2.16	0.06
		Paracentral	4	288	12	−34	55	0.21	0.45	−1.41	0.19
		Precentral	6	294	33	−13	39	0.31	0.53	−1.62	0.14
		Superior frontal	9	191	31	34	30	0.46	0.41	0.32	0.76
			10	118	23	50	9	1.30	0.06	2.94	0.02[b]
Limbic		Ant. cingulate	32	513	10	9	47	0.59	0.58	0.08	0.94
Parietal		Postcentral	43	154	50	−14	18	−0.14	0.59	−2.93	0.02[b]
		Precuneus	7	139	7	−52	39	0.84	0.27	2.88	0.02[b]
		Supramarginal	40	229	42	−51	31	0.63	0.83	−0.59	0.57
				137	54	−49	29	0.46	0.66	−0.86	0.41

[a]mm³=cluster volume in cubic-millimeters; RL=left (−) to right (+) orientation in relation to midline; AP=anterior (+) to posterior (−) orientation in relation to the anterior commissure (AC); IS=inferior (−) to superior (+) in relation to the AC-PC line; Ant.=Anterior.
[b]Significantly greater activation at Time 1 (positive *t* values) relative to Time 2. *Z* scores reflect mean activation change for each group in that particular cluster. Mean *Z* scores for these clusters are Time 1=0.625 and Time 2=0.506.

Behavioral-activation relationships

Correlations were computed between performance at Time 1 and Time 2 and the corresponding functional activation in each of the clusters extracted for the Older Adult Retest. Because of the small sample size, traditional correction for multiplicity of tests here is not possible and these analyses must be interpreted with caution. To attain some degree of certainty about the stability of behavior-activation relationships over time, correlations had to be in the same direction and of similar magnitude. No clusters had significant correlations at Time 1 and Time 2. Two of the 26 comparisons had one cluster above an $r = 0.45$ threshold at either Time 1 or Time 2, and another cluster at least above 0.30 at the other time that had the same directionality. These clusters were in the right medial frontal gyrus (BA 6, Time 1 $r = 0.302$, $P = 0.397$, Time 2 $r = 0.565$, $P = 0.089$), and the right supramarginal gyrus (BA 40, Time 1 $r = 0.383$, $P = 0.275$, Time 2 $r = 0.471$, $P = 0.17$).

Discussion

The present study was conducted to determine whether activation differences between younger and older adults in inhibitory control could be replicated, and to determine the consistency of older adult activation over time. A comparison of the present results with prior results (Nielson et al., 2002) indicated a high degree of similarity of the areas of activation for older and younger adults. Specifically, the primary areas of activation in both studies were in bilateral inferior and middle frontal gyri, inferior parietal areas, and anterior cingulate gyri and supplementary motor area, as well as the left insula, claustrum, and putamen. As is shown in Fig. 1, 20 of 23 clusters in the current study were comparable or identical to clusters reported in the previous study (Nielson et al., 2002). Furthermore, the regions of interest derived from the present study and the previous study are highly consistent with the existing inhibitory control literature (Garavan et al., 1999; Konishi et al., 1998, 1999; Rubia et al., 2001; Watanabe, 1986a, 1986b). Therefore, the results for this Go/No-go task during fMRI are similar to the published literature in location of functional activation foci and are repeatable with older adults.

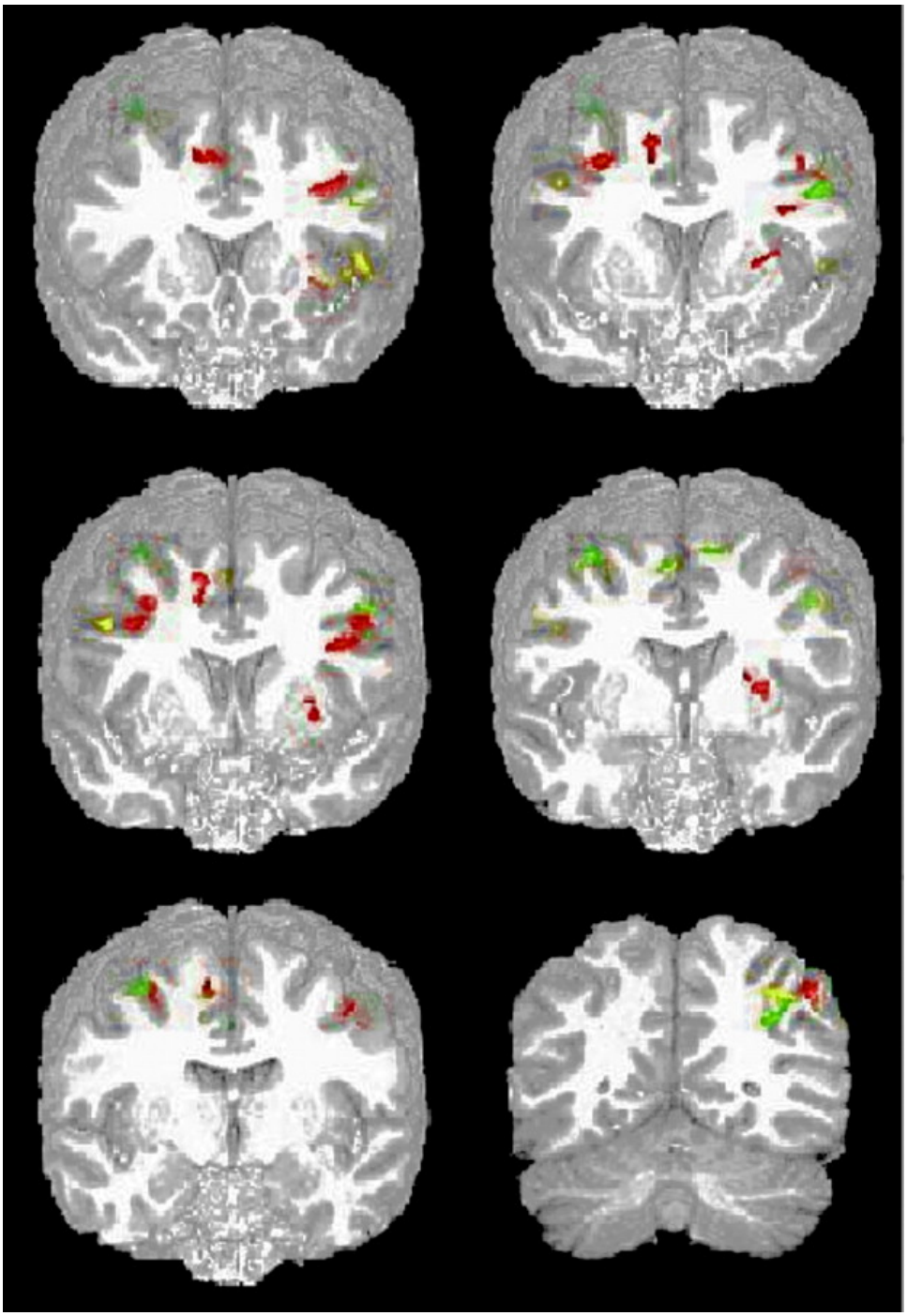

Fig. 1. Significant activation for older adults at Time 1 (yellow, Table 4) and at Time 2 (red, Table 2 and Table 4). These clusters are derived separately for each time and do not indicate the direction of differences between older adults at Time 1 and Time 2. The six clusters in Table 3 are depicted in green (the direct *t* test for all voxels between Time 1 and Time 2). Pictures are from left to right and top to bottom at 13 (anterior), 8, 5, −1 (posterior), −6, and −57 mm from the anterior commissure. Coronal images are in standard radiological orientation (right is left) and are at an angle of 110° (tilted forwards) from the AC-PC line.

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The older adult's performances on the Go/No-go task were comparable at Time 1 and Time 2, indicating no decline over the elapsed time. However, the young group in the present study performed significantly more poorly than the young group in the previous study. As a result, the present study did not replicate findings of decreased inhibitory control in older adults. The difference between the young groups is likely due to sampling variability. It could be suggested that the difference in the length of the task due to the change in number of runs (see materials and methods) could be at fault, but it is unclear why this change would only have affected the young group. Additionally, the data for the present study were collected in the late morning and early afternoon hours, while the data for the previous study were collected in the late evenings, due to scanner availability. Time of day has been shown to affect cognitive performance, and the optimal time of day differs in young and older adults (May et al., 1995). The original study was conducted at a more optimal time of day for young adults, but the current study was done at a less optimal time of day for young adults and a more optimal for older adults. Again, however, this factor would have been expected to affect both young and older adults. Moreover, regardless of the performance differences, correctly performed trials used in the functional analyses produced comparable areas, magnitudes, and group differences in activation across studies. This finding lends confidence to conclusions about compensatory activation in older adults particularly in left prefrontal regions that have been the focus of some debate (DiGirolamo et al., 2001; Jonides et al., 2000; Nielson et al., 2002; Rypma and D'Esposito, 2000). The absence of a behavioral effect in the presence of a functional activation effect between groups could be used to argue that the activation differences between groups are more likely the result of an age effect, and not a performance effect.

It was expected that in addition to convergence in location of significant clusters and direction of differences between younger and older adults, there would also be equivalence in activation from Time 1 to Time 2 for older adults. This hypothesis was confirmed. There were only a few clusters, predominantly in prefrontal regions, that were significantly more active at Time 1 than at Time 2. In each of these cases, the clusters at Time 2 were significantly active, but less so than at Time 1. The reasons for this difference are not known, although it

could be due to greater task difficulty at Time 1, although inhibition performance at the two time points was not significantly different. There are also possible effects of novelty and habituation (Fischer et al., 2003; Kiehl and Liddle, 2003; Loubinoux et al., 2001) and procedural learning (Eliassen et al., 2001) that could account for these minor differences between Time 1 and Time 2. Another possibility is that the use of four separate trial blocks at Time 1 (i.e., a longer task with more events) and a larger participant pool resulted in a higher signal to noise ratio than with two blocks at Time 2, which would have enabled better differentiation of significantly active clusters and greater inhibition-related activation compared to baseline.

Correlations between performance and normalized activation values were computed for the older group at Time 1 and using both sets of clusters (Tables 3 and 4) from Time 2. Previous studies have reported significant correlations with performance and behavior in the right medial frontal gyrus and right supramarginal gyrus, indicative of their importance in successful inhibitory control (Garavan et al., 1999; Humberstone et al., 1997; Rubia et al., 2001). The present study demonstrated correlations in this same direction, but the experimental design was weak for investigating this topic and the results gave little confidence regarding a strong relationship between activation and task performance. Indeed, there was not a great deal of consistency in correlations with Time 1 and Time 2 data. Although the sample is too small to adequately investigate this idea, it is possible that nonlinear analyses would better reveal activation-behavior relationships. Future studies may benefit from including a larger number of events (i.e., trials) of interest, shorter and a larger number of trial blocks, and larger participant pools to increase signal-to-noise ratio. Inhibitory performance was generally stable for this group of older adults over a 14-month period, suggesting that this task would be useful for test-retest comparisons, perhaps before and after a treatment to enhance inhibitory control performance.

In summary, the present study replicates previous findings of important inhibition-related brain areas in right frontal and parietal cortex areas. Furthermore, it replicates prior results suggesting more bilateral activation in older adults compared to unilateral activation in younger adults (Cabeza et al., 1997a; Grady et al., 1994; Madden et al., 1997, 1999; Nielson et al., 2002; Schachter et al., 1996).

Activation increases in the right medial frontal gyrus and the right supramarginal gyrus were consistently related to good inhibitory performance. Finally, performance and activation appear stable and repeatable over time in healthy older adults, although some predominantly frontal regions are more strongly activated at first test than at retest. The results strengthen confidence about the circuitry associated with inhibition and the findings of compensatory activation in older adults in various studies using different tasks and methods.

Acknowledgements

We are grateful for the technical assistance of Dr. Thomas J. Ross, and the assistance with data collection by Benjamin Bock, Kirk Erikson, Douglas Yee, and Ted Bryant. This work was supported in part by a Dissertation Research Award from the American Psychological Association (to S.A.L.) and by the Foley Center for Aging and Development, Medical College of Wisconsin, WI, USA (to K.A.N.).

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