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Age-related differences in effective neural connectivity during encoding and recall

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AGE-RELATED differences in brain activity may reflect local neural changes in the regions involved or they may reflect a more global transformation of brain function. To investigate this issue, we applied structural equation modeling to the results of a positron emission tomography (PET) study in which young and old adults encoded and recalled word pairs. In the young group there was a shift from positive interactions involving the left prefrontal cortex during encoding to positive interactions involving the right prefrontal cortex during recall, whereas in the old group frontal interactions were mixed during encoding and bilaterally positive during recall. The present results suggest that age-related changes in neural activation are partly due to age-related changes in effective connectivity in the neural network underlying the task.

Key words: Aging; Covariances; Encoding; Episodic memory; Functional neuroimaging; Network; Positron emission tomography; Recall; Retrieval; Structural equation modeling

Introduction

Many cognitive functions, and memory in particular,[1] show a clear decline in old age. This decline seems to be a consequence of the anatomical and physiological deterioration suffered by the brain as an effect of the aging process.[2–4] Positron emission tomography (PET) studies have demonstrated regional age-related decreases in neural activity during the performance of cognitive tasks.[5–8] It is unclear, however, whether these regional differences in activation reflect a local neural deterioration in the regions involved (e.g. the right anterior prefrontal cortex[7,8]) or whether they reflect a more global transformation of brain function. This issue is of particular importance in the case of crossover age × task interactions. In our previous study,[8] for example, a left prefrontal region (area 47) was more active during encoding than during recall in young adults, but it was more active during recall than during encoding in old adults. It is difficult to interpret this result in terms of a local neural phenomenon, since the same region was less activated or more activated in old adults depending on the task. In contrast, this kind of finding suggests a global change in which the same region can have different roles in the two age groups depending on its interactions with other regions within the network subserving the task. The present study investigated this alternative.

The standard method of analyzing positron emission tomography (PET) data, the subtraction method, provides an indication about the brain regions active in certain tasks, but not about the functional interrelations between them. In order to investigate these interrelations, we applied structural equation modeling (also called path analysis) to the results of a PET experiment. Path analysis can reveal how a set of brain regions influence one another during a certain task and how these influences change across tasks.[9–12] Path analysis combines inter-regional covariances with an anatomically defined network and can be regarded as a tool to measure effective connectivity,[9,13] or the direct effect one region has on another. We expected that path analysis would clarify the origin of the aforementioned age × task interaction. More generally, we investigated the hypothesis that age-related changes in activation during a certain task are partly due to an age-related reorganization of neural systems underlying the task.

Materials and Methods

The behavioral and PET methods were described previously,[8] and a brief summary is provided here. The study was approved by the joint Baycrest Centre/University of Toronto Research Ethics and Scientific Review Committee The subjects were 12 young (mean 26 years) and 12 old (mean 70 years)

healthy right-handed adults. They showed similar recall performance during the scans, but the old group had significantly poorer performance on the California Verbal Learning Test. The materials were word pairs, such as 'parents–piano'. Two conditions were selected from the original study: encoding and recall. In the encoding condition, subjects tried to learn each pair by noting associations between the two words, and read the second word aloud. In the recall condition, they were presented with the first word of each pair and the word 'word', and had to recall the second word. If they could recall it, they said it aloud; if not, they said 'pass'. Each condition was scanned twice with a bolus injection of $[O^{15}]H_2O$. The images were corrected for between scan movement, stereotaxically normalized, and spatially filtered (10 mm isotropic Gaussian) using SPM95.[14] Analyses were performed for the main effects of encoding and recall collapsed over groups and for the group × task interaction. A full exposition of the activation analysis has been presented elsewhere.[8]

The path analysis involved six steps. (1) Thirteen regions were selected from those showing the largest regional cerebral blood flow (rCBF) differences in the subtraction analysis (see right-hand column of Table 1). When a main effect and an interaction occurred in nearby regions, the interaction was preferred (e.g. left Brodmann area 6–L6, L47 in Table 1). Some regions, such as the cerebellum, were not included because it was felt that the model would become too complicated. (2) The 13 selected regions were linked to each other on the basis of known neuroanatomy[15–17] to create an anatomical model (see Fig. 1). (3) rCBF correlations among the 13 regions were calculated. Before computing the correlations, the value for each pixel in the images of each subject was divided by the average global CBF for the subject in the task, and reduced by the average value for the pixel across all tasks. (4) Structural equation modeling (LISREL 8) was applied to the rCBF correlations among the regions. Structural equation modeling, or path analysis, is a method to calculate the value or weight that each path in a causal model should have for the model to account for the observed pattern of covariances. The paths are assigned starting values, which are then modified through a process of iterative data fitting until an optimal solution is achieved. The resulting path coefficients can be interpreted in a manner similar to regression coefficients. In the present application, for example, a positive path coefficient means that a unit increase in the activation of one region leads to a direct increase in the activation of the region it projects to, proportional to the size of the coefficient. Conversely, a negative path coefficient means that an increase in the activation of one structure leads to a direct, proportional decrease in the activation of the structure it projects to.

Table 1. PET Activations

Region	BA	x	y	z	Z-scores	SEL
Main effect of task						
Encoding minus recall						
Right sylvian	42	52	–18	8	6.0	R42
Left temporal	22	–40	–26	–16	4.9	L20
Right temporal	37	44	–72	4	4.9	R37
Left prefrontal	6/8	–28	12	44	4.9	
Recall minus encoding						
Right prefrontal	47	32	16	–4	5.6	R47
Left prefrontal	47	–34	12	–4	5.4	
Anterior cingulate	32	6	36	20		aci
Midbrain		–2	–34	–12	5.1	
Right prefrontal	10	20	56	0	4.7	R10
Right parietal	39	42	–68	32	4.7	
Cerebellum		0	–56	–24	4.4	
Thalamus		4	–12	0	4.4	th
Right temporal	20	58	–34	–12		
Posterior cingulate	23	–2	–28	32	4.2	pc
Task × age interactions						
YE > YR OE < OR						
Anterior cingulate	32	10	12	44	4.2	acs
Left sylvian	42	–62	–32	8	4.1	L42
Left prefrontal	6	–50	2	20	4.0	L6
Left prefrontal	47	–36	28	0	4.0	L47
YE < YR OE > OR						
Right prefrontal	9	12	54	28	4.1	R9
Right caudate		–10	20	0	4.0	

Coordinates (x,y,z) and Brodmann's areas (BA) from Ref. 24. The z-scores correspond to pairwise contrasts between encoding and recall conditions, or to the task × age interactions. YE, young-encoding; YR, young-recall; OE, old-encoding; OR, old-recall; SEL, regions selected for path analysis.

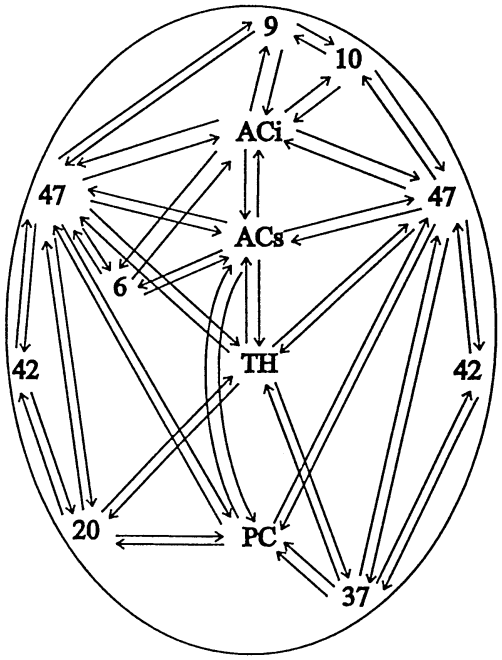

FIG. 1. Anatomical model linking 13 selected regions (see rightmost column of Table 1).

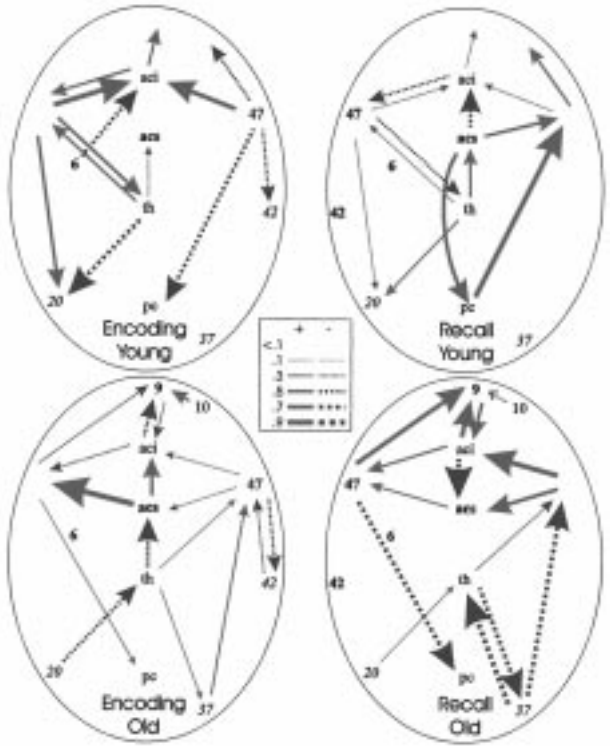

FIG. 2. Path coefficients that showed a difference of > 0.50 between encoding and recall conditions. Positive coefficients appear in solid red arrows and negative coefficients in segmented blue arrows, with the thickness of the arrows representing the magnitude of the coefficient.

Feedforward path coefficients (i.e. paths pointing toward a more anterior region) were computed first, and then backward path coefficients (i.e. paths pointing toward a more posterior region) were calculated taking into account the estimates of the feedforward paths.[18] The assumption of the present model is that feedback effects depend on feedforward influences. We acknowledge that alternative solutions may be possible with other assumptions, but the present model is appropriate to determine whether the different patterns of activation observed between groups can be explained by different functional interactions within the same model. (5) In both groups, the solution was constrained to be equal between conditions, the fit assessed, and then the constraint removed. If the fit improved when an independent solution was calculated, a significant change in the network between encoding and recall conditions was assumed. (6) The largest changes in path coefficients (thresholded arbitrarily at a difference > 0.5) between encoding and recall conditions were identified in both groups (see Fig. 2).

Results

The results of the subtraction analysis are reported in Table 1. Compared with recall, encoding was associated with increased rCBF in right Sylvian (R42), bilateral temporal (L20, R37), and left prefrontal regions. Compared with encoding, recall was associated with activations in several regions including prefrontal, inferior anterior cingulate (ACi), posterior cingulate, and thalamic (TH) regions. Prefrontal activations were more pronounced in right hemisphere (R47, R10) during recall. Some regions were more active during encoding than during recall in the young but showed the converse tendency in the old. These included superior anterior cingulate (ACs), left Sylvian (L42) and left prefrontal (L6, L47) regions. The task × age interaction was striking in left area 47 (L47). Finally, other regions tended to be more activated during recall than during encoding in the young but not in the old, such as right area 9 (R9). The 13 regions indicated in the rightmost column of Table 1 were included in the model for path analysis.

The results of the path analysis are reported in Table 2. The difference between the solution for the encoding and recall conditions was significant in both the young group (χ^2diff(34) = 90, $p < 0.001$) and the old group (χ^2diff(34) = 116, p 0.001). Figure 2 shows for each group those path coefficients that showed the largest encoding/recall differences (diff. > 0.5). In the young group, there was a dissociation between the functional interactions of L47 and R47 between tasks: whereas L47 interactions tended to be positive during encoding and negative during recall, R47 interactions tended to be negative during encoding

Table 2. Path Coefficients

Encoding-Young

	L20	pc	R37	L42	th	R42	acs	aci	L6	L47	R47	R10	R9
L20		-.06		-.27	-.69					.48			
pc	.20		.25				.02			-.51	-.59		
R37		-.12			.24	.31					.25		
L42	-.01									.23			
th	-.10		.38				-.21			.48	.23		
R42			.52								-.41		
acs		-.18			-.22			-.05	.18	-.01	-.31		
aci							-.03		-.63	.75	.68	-.06	.18
L6							.27	-.47		.33			
L47	.34	-.13		.07	.36		.21	.43	.36				.16
R47		.06	.24		.07	-.31	-.02	.80				-.32	
R10								-.42			-.35		-.46
R9								.40		-.05		-.59	

Recall-Young

	L20	pc	R37	L42	th	R42	acs	aci	L6	L47	R47	R10	R9
L20		-.03		-.06	.25					-.15			
pc	.04		-.14				.57			-.14	.08		
R37		-.33			-.07	.28					-.02		
L42	-.14									-.10			
th	.30		.19				.14			-.41	-.15		
R42			.28								.28		
acs		.27			.35			-.28	-.05	.06	-.28		
aci							-.62		.07	-.15	-.17	-.06	.01
L6							.06	-.13		.35			
L47	.08	-.08		.09	-.20		.05	-.42	.35				-.03
R47		.77	-.05		-.36	-.40	.50	.92				.15	
R10								-.20			.40		.13
R9								-.15		-.16		.30	

Encoding-Old

	L20	pc	R37	L42	th	R42	acs	aci	L6	L47	R47	R10	R9
L20		-.14		.23	-.29					-.18			
pc	-.24		-.36				.37			.18	.10		
R37		-.10			.24	.27					.33		
L42	.43									.22			
th	-.49		-.06				-.10			-.15	-.14		
R42			.16								-.40		
acs		.00			-.57			.08	-.28	-.02	-.23		
aci							.49		.07	-.18	-.23	.27	-.29
L6							-.50	.03		.38			
L47	-.10	-.08		.40	.16		.89	-.34	.14				-.17
R47		.34	.26		.22	-.27	-.14	.15				.25	
R10								.51			.38		.18
R9								-.51		-.26		.35	

Recall-OLd

	L20	pc	R37	L42	th	R42	acs	aci	L6	L47	R47	R10	R9
L20		-.45		.17	-.40					-.25			
pc	-.48		.12				-.06			-.67	.29		
R37		-.36			-.67	-.20					-.07		
L42	.14									.57			
th	.21		-.80				-.18			.14	.20		
R42			-.05								.93		
acs		-.22			.09			-.78	-.02	.07	.61		
aci							-.07		.26	.12	.82	.02	.51
L6							-.04	.50		.26			
L47	-.31	.22		.60	.35		.32	.41	.12				-.09
R47		-.11	-.66		-.30	.65	-.18	.63				.35	
R10								.71			.14		.13
R9								.66		.65		-.32	

Each coefficient correspond to the path going from the region indicated in the column heading to the region indicated in the row heading.

and positive during recall. Another large difference in the young group occurred among right frontal areas: R47, R10, and R9 were connected by negative paths during encoding but by positive paths during recall. In the old group, the interactions of both L47 and R47 were mixed (i.e. were both positive and negative) during encoding and mainly positive during recall. In this group, the effect of R10 on R9 was positive during encoding and negative during recall, a shift in the opposite direction than the one observed in the young subjects. Finally, paths involving R37 were mainly positive during encoding and mainly negative during recall in the old subjects, whereas in young adults these paths showed little or no change across tasks.

Discussion

The results of the path analysis were generally consistent with the activation data. In particular, the path analysis provided two main results. First, in the young group there was a shift from positive interactions involving the left prefrontal during encoding to positive interactions involving the right prefrontal during recall, whereas in the old group frontal interactions were mixed during encoding and bilaterally positive during recall. This pattern is consistent with the finding that frontal activity in young adults was left-lateralized during encoding and right-lateralized during recall, whereas old adults showed little frontal activity during encoding and a more bilateral pattern of frontal activation during recall.[8] The lateralized pattern shown by young subjects is typically observed in PET studies of episodic memory and it has been described in terms of a 'hemispheric encoding/retrieval asymmetry' (HERA) model.[19,20] The activation and path analysis results indicate that this pattern does not hold in old age. The involvement of the left prefrontal during recall in old adults may reflect functional reorganization. One possibility is that old adults may have compensated for deficits in episodic retrieval operations involving the right prefrontal cortex by recruiting semantic retrieval operations tapping the left prefrontal cortex (see Ref. 8). The interactions seen between right and left prefrontal regions in the old subjects during recall is generally consistent with this idea. It is likely that neural changes in old adults are accompanied by a reorganization of function like that observed after brain damage.[21,22] The present results suggest that this change is not merely local, but involves a more global reorganization of the networks subserving cognitive performance.

The second main result of the path analysis is that, in the young group, right frontal areas 9, 10, and 47 were negatively associated during encoding and positively associated during recall. In the old group, area 10 had a positive influence on area 9 during encoding and a negative influence during recall. This result is consistent with the finding that the right prefrontal cortex, and particularly area 9, was less activated during recall in old than in young adults. One

possible explanation suggested by the present results is that in young adults right frontal regions have a cooperative relation during recall, while in old adults they are less integrated and perhaps functionally disconnected.

The significance of the present study does not lie in particular changes in path coefficients, but in providing support for the general hypothesis that age-related changes in activation are partly due to age-related changes in effective connectivity. Although there are age-related changes in specific structures,[23] these changes result in a global transformation of the networks subserving various cognitive operations. For example, the age × task interaction in left frontal area 47 related well to the different interactions of this region with other brain areas seen in young and old adults. This difference may reflect an alternate role for this region, in the old subjects, within the functional network usually engaged to perform the encoding and recall tasks. A difference in strategy is another possible interpretation, but not a likely one, at least during the encoding condition, since an encoding strategy was provided to both groups of subjects. The task of understanding specific age-related changes in effective connectivity is formidable, but the present research encourages the belief that it is possible to explore such changes and potentially relate them to different cognitive phenomena.

Conclusion

We began with the hypothesis that age-related changes in brain activation during a certain task are partly due to age-related changes in effective connectivity in the neural network underlying the task. Using path analysis to combine an anatomical model with the inter-regional covariances of activity, we were able to provide confirmation for this hypothesis showing how the group differences in effective connections between regions map to the differences in activation. Finally, we suggested that the exploration of functional network interactions might provide a more veridical picture of the biological substrates of cognition and how these change with age.

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