ORIGINAL CONTRIBUTION

Association of Life Activities With Cerebral Blood Flow in Alzheimer Disease

Implications for the Cognitive Reserve Hypothesis

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Background: Regional cerebral blood flow (CBF), a good indirect index of cerebral pathologic changes in Alzheimer disease (AD), is more severely reduced in patients with higher educational attainment and IQ when controlling for clinical severity. This has been interpreted as suggesting that cognitive reserve allows these patients to cope better with the pathologic changes in AD.

Objective: To evaluate whether premorbid engagement in various activities may also provide cognitive reserve.

Design: We evaluated intellectual, social, and physical activities in 9 patients with early AD and 16 healthy elderly controls who underwent brain $H_2{}^{15}O$ positron emission tomography. In voxelwise multiple regression analyses that controlled for age and clinical severity, we investigated the association between education, estimated premorbid IQ, and activities, and CBF.

Results: In accordance with previous findings, we replicated an inverse association between education and CBF and IQ and CBF in patients with AD. In addition, there was a negative correlation between previous reported activity score and CBF in patients with AD. When both education and IQ were added as covariates in the same model, a higher activity score was still associated with more prominent CBF deficits. No significant associations were detected in the controls.

Conclusions: At any given level of clinical disease severity, there is a greater degree of brain pathologic involvement in patients with AD who have more engagement in activities, even when education and IQ are taken into account. This may suggest that interindividual differences in lifestyle may affect cognitive reserve by partially mediating the relationship between brain damage and the clinical manifestation of AD.

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THE COGNITIVE reserve (CR) hypothesis suggests that there are individual differences in the ability to cope with the pathologic changes in Alzheimer disease (AD).[1] Innate intelligence or aspects of life experience may supply reserve in the form of a set of skills or repertoires that allow some people to cope with the pathologic changes better than others. Educational and occupational attainments are considered such aspects of life experience.

Epidemiologic data supporting the CR hypothesis include observations that higher educational and occupational attainment is associated with decreased risk for incident dementia.[2] Functional imaging studies have also provided support for the concept of CR. Considering cerebral blood flow (CBF) as an indirect index of pathologic changes in disease[3-10] (lower blood flow indicating more advanced pathologic changes in AD) studies have shown that patients with higher educational[11] or occupational[12] attainment as well as those with a higher premorbid IQ[13] have more prominent flow deficits when controlling for clinical severity. These flow deficits were located in the brain regions typically associated with reduced CBF in AD. Again, these observations support the prediction that individuals with more CR can tolerate more pathologic changes. Factors other than education and occupation might also provide reserve against pathologic changes in AD. Both cross-sectional and prospective longitudinal studies have suggested that engaging in various social, intellectual, and leisure activities is associated with reduced risk of prevalent or incident AD.[14-18]

The present study was designed to use the functional imaging approach just described to clarify the role of reported activities in CR. We evaluated intellectual, social, and physical activities in patients with AD who underwent brain $H_2{}^{15}O$ positron emission tomography (PET). A role for such activities in CR would predict that, when controlling for disease severity, patients with

Table 1. Items Included in the Activities Scale

During the Last 6 Months Did You . . . (Never = 1, Sometimes = 2, Often = 3)
Watched television or listen to the radio
Play cards or other games
Read books, magazines, or newspapers
Go to lectures or concerts
Go to theater or movies
Travel or go on tours
Go for walks or rides
Take part in sports, dancing, or exercise
Do gardening
Spend time being alone
Do arts and crafts or hobbies
Cook or prepare food as a hobby
Collect things as a hobby
Sing or play a musical instrument
Visit or were visited by friends or relative or neighbors
Participate as a member of a club or organization
Participate in church or religious activities
Do other volunteer work and have time to be alone

higher activity scores would have more advanced pathologic changes in AD. Thus, using CBF as an indirect indicator of pathologic changes in disease would show a negative correlation between activity scores and CBF in areas of the brain that typically show reduced CBF in AD.

METHODS

SUBJECTS

Nine patients who met *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*) criteria for dementia[19] and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association for probable AD[20] and 16 healthy elderly controls participated in this study. The patients underwent extensive neuropsychologic evaluation, including the Wechsler Adult Intelligence Scale–Revised,[21] the American version of the Nelson Adult Reading Test (NART) estimated IQ,[22-24] the modified Mini-Mental State examination (mMMS),[25-27] and tests of memory (short- and long-term verbal[28] and nonverbal[28,29]), orientation, abstract reasoning (verbal[21] and nonverbal[30]), language (naming,[31] verbal fluency,[32,33] comprehension,[33] and repetition[33]), and construction (copying[34] and matching[29]). In addition, the Blessed Dementia Rating Scale (part I, sections A and B)[35] was administered. Magnetic resonance imaging (MRI) was used to rule out patients with vascular diseases or tumors. Other causes of dementia were excluded with appropriate laboratory tests. The diagnosis of AD was reached at a consensus diagnostic conference of physicians and neuropsychologists. Positron emission tomography results did not play any role in the diagnostic process.

ACTIVITIES

Before the PET scan, an interview with the patient and the informant or the healthy subject assessed activities engaged in during the last 6 months. The questionnaire was an expanded version of a scale administered to a community of 1772 elderly subjects in a prospective incidence dementia study.[18] Participation in 18 activities was recorded (**Table 1**). The sum of the points over the 18 activities was calculated for each patient and this leisure score was used as a predictor in subsequent analyses. It was also recorded whether the amount of time patients had spent doing each activity had decreased, remained the same, or increased during the previous 10 years.

PET SCAN ACQUISITION AND PROCESSING

Scans were collected while the subject was at rest with eyes closed. For each scan, a bolus of 30 mCi (1110 MBq) of intravenous $H_2{}^{15}O$ was injected. Using an EXACT 47 PET camera (Siemens, Knoxville, Tenn), three 30-second scan frames were acquired in 2-dimensional mode beginning 20 seconds after tracer administration. After measured attenuation correction (15-minute transmission scan) and reconstruction by filtered back-projection, image resolution was 10 mm full width at half-maximum (FWHM). Arterial blood sampling was not conducted; thus, nonquantitative count images (and not absolute CBF measures) were obtained.

Using modules from the statistical parametric mapping program (SPM99; Wellcome Department of Cognitive Neurology, London, England), the following steps were performed in turn for each subject: (1) The 3 PET frames were realigned to each other and summed. (2) A T1-weighted MRI was coregistered to this summed PET image. Magnetic resonance images were acquired using a 1.5-Tesla MR scanner. A T1 3-dimensional spoiled-gradient-recalled echo sequence (repetition time [TR] = 34 ms; echo time [TE] = 5 ms; flip angle = 45°) was used to acquire T1-weighted images with an in-plane resolution of 0.859 mm × 0.859 mm (256 × 256 matrix; 22 cm^2 field of view). One hundred twenty four –1.5-mm transaxial slices were acquired. The z-dimension was down-sampled to a final dimension of 6 mm per slice. (3) The coregistered MRI was spatially transformed to the coordinates defined by the Montreal Neurological Institute template brain provided by SPM99. (4) The spatial normalization parameters were applied to the summed PET image, which was resliced using sinc interpolation to a final voxel size of 2 mm × 2 mm × 2 mm. (5) The spatially normalized PET image was intensity normalized by its average perirolandic count value (given that both pathologic and quantitative PET CBF imaging data suggest that the perirolandic cortex is typically spared by pathologic changes in disease[8,10,36,37]). (6) The spatially and intensity normalized PET image was spatially smoothed with an isotropic Gaussian kernel (FWHM = 8 mm).

STATISTICAL ANALYSES

Various voxelwise multiple regression analyses[38] were performed on the intensity normalized images (subsequently referred to as "CBF" with the understanding that they are not in physiologic units). Values of the CBF were used as the dependent variable in all of the multiple regression models.

Several regression models were separately estimated. Putative CR variables in these various models included education, estimates of premorbid IQ, and the activity score. Word-reading ability as assessed by NART was used to estimate premorbid IQ. Performance on this task remains relatively preserved in mild AD and is considered a good estimate of premorbid abilities.[39] The score on the mMMS was used as an index of the clinical severity of dementia.[25,26,40]

Our strategy for the regression analyses was to first assess the association between CBF and each putative CR variable individually. We controlled for age[41] and mMMS score (ie, clinical severity) in all of the models. We first introduced years of education and NART score (in 2 separate models) as independent variables to replicate previous findings. We then used the activity score as an independent variable in a separate model. We finally sought to explore whether there was a relationship between CBF and activity score while accounting for the other variables (education and NART score).

Table 2. Demographic, Clinical, and Neuropsychologic Data for 9 Patients With Alzheimer Disease

	Patient No.								
	1	2	3	4	5	6	7	8	9
Age, y	67	76	63	86	52	55	85	49	85
Duration of disease, y	1	2	5	7	3	3	4	3	10
Education, y	12	8	19	14	18	16	16	18	14
NART score	92	105.4	122	115	122.5	99.4	114.9	121.6	121.2
Activity score	28	32	39	39	37	36	37	36	39
mMMS score	42	46	51	41	34	37	43	49	53
SRT total recall	30	36	44	26	10	30	25	30	32
SRT delayed recall	1	4	4	2	0	1	4	2	6
Phonological fluency, percentile	38	10	34	56	39	10	12	99	90
Categorical fluency, percentile	1	9	56	15	20	2	1	3	19
Blessed Dementia Rating Scale	1.5	2	1.5	2	2	0.5	1.5	2	1

Abbreviations: mMMS, Mini-Mental State examination; NART, Nelson Adult Reading Test; SRT, Selective Reminding Test.

For each regression model, voxelwise relationships between the scaled count values and the independent variables of interest were calculated and statistically assessed with *t* values.[38] The false-positive rate was controlled at $\alpha = .05$ per map via Bonferroni correction for the number of statistically independent resolution elements (resels) across which regressions were calculated (number of resels = total volume of map / product of FWHM across x, y, and z dimensions).[42]

We used the tissue density values from subjects' MRI results (in voxels where significant associations were noted in the previous analyses) as covariates in the regression analyses to explore the possibility that any associations between the CR variables and CBF are mediated by atrophy. The atrophy analyses did not change the results.

RESULTS

DEMOGRAPHICS, LEISURE SCORES, AND CR SUMMARY MEASURES

Demographic, clinical, and neuropsychologic variables for each of the AD subjects are presented in **Table 2**. The same data are presented for both patients with AD and controls in **Table 3**. There were 5 men and 4 women in the AD group and 6 men and 10 women in the control group.

Although all of the test subjects had only mild AD, it could be argued that current activities do not accurately reflect premorbid lifestyle. We therefore examined the reported change in the amount of time spent doing each activity during the last 10 years. For 5 patients, the time spent on each activity was reported to have either increased or remained stable over the last 10 years. Four patients reported decreased time devoted to 2 of 18, 3 of 18, 4 of 18, and 6 of 18 activities, respectively. Since these activities represented only a small fraction of the overall score, with most of the activities exercised at a stable rate or more frequently, we considered the activity score to be a reasonable estimate of activities, at least during the decade preceding the study.

Correlations between education and NART score were $r = 0.59$, $P < .002$ (AD: $r = 0.60$, $P < .09$; control: $r = 0.67$, $P < .004$); between education and activities, $r = 0.29$, $P < .15$ (AD: $r = 0.60$, $P < .08$; control: $r = -0.15$, $P < .59$); and between NART score and activities, $r = 0.53$, $P < .007$ (AD: $r = 0.81$, $P < .008$; control: $r = -0.05$, $P < .85$). The nonsignificant correlations may indicate that the variables are not truly associated. Nevertheless, it is hard to draw many conclusions from this given the very small number of subjects (9 patients with AD and 16 controls), which may have resulted in low power to detect existing significant correlations.

Table 3. Demographic, Cognitive, and Functional Characteristics of the Subjects*

Characteristic	Alzheimer Disease (n = 9)	Control (n = 16)	*P* Value
Age, y	68.8 (14.9)	76.6 (6.3)	.16
Duration of disease, y	4.2 (2.8)	NA	NA
Education, y	15 (3.5)	15.3 (2.0)	.82
NART score	112.6 (11.2)	119.8 (6.1)	.11
Activity score	35.9 (3.7)	37.9 (2.4)	.12
mMMS score	43.9 (6.3)	51.9 (3.4)	.006
SRT total recall	29.2 (9.2)	48.8 (8.7)	.001
SRT delayed recall	2.7 (1.9)	7.7 (3.0)	.001
Phonological fluency, percentile	43.1 (33.1)	75.7 (22.4)	.009
Categorical fluency, percentile	14 (17.5)	54.1 (24.7)	.001
Blessed Dementia Rating Scale	1.6 (0.5)	0.15 (2.4)	.001

Abbreviations: mMMS, Mini-Mental State examination; NA, not applicable; NART, Nelson Adult Reading Test; SRT, Selective Reminding Test.
*Data are given as mean (SD) unless otherwise indicated.

REGRESSION ANALYSES

In accordance with previous findings,[11] education was inversely associated with CBF (**Table 4**). Similarly, in line with previous reports,[13] there was a negative association between premorbid IQ (as measured by the NART) and CBF (Table 4).

The activity score was also inversely correlated with CBF when controlling for age and mMMS score (**Table 5** and **Figure**). Significant associations were localized mainly to the temporal lobe but also in temporal-parietal-occipital association areas. When simultaneously controlling for age, mMMS score, education, and NART score, activity score was still negatively correlated with CBF (**Table 6**).

Table 4. Local Maxima With Statistically Significant Inverse Association Between Cerebral Blood Flow (CBF) and Education and Between CBF and Nelson Adult Reading Test Score*

	Talairach Coordinates				
	x	y	z	*t* Values	Locations (Brodmann Area)
Education					
Alzheimer disease					
	−10	−58	45	5.2†	Precuneus (7)
	26	16	45	4.8†	Middle frontal gyrus (8)
	50	−69	22	4.5‡	Middle temporal gyrus (39)
Control					
	. . .	. . .	. . .	. . .	. . .
Nelson Adult Reading Test score					
Alzheimer disease					
	14	1	17	6.0‡	Caudate
	20	−7	24	5.3‡	Cingulate
	20	−13	12	5.1†	Thalamus
	−34	−34	50	5.6‡	Parietal-postcentral gyrus (3)
	−32	−24	−9	5.4‡	Hippocampus
	−12	−41	39	5.4‡	Cingulate (31)
	8	4	5	5.2†	Caudate
	8	−2	0	4.9†	Lentiform nucleus
	18	−68	29	5.1†	Precuneus (7)
	12	−12	−13	4.8†	Brainstem
	36	−20	−16	4.7†	Parahippocampal gyrus
	−14	29	2	4.7†	Cingulate-corpus callosum
	−24	35	41	4.6†	Middle frontal gyrus (8)
Control					
	. . .	. . .	. . .	. . .	. . .

*The analyses were controlled for age and Mini-Mental State examination score. Ellipses indicate that significant inverse associations were detected for the controls. No positive associations were detected for either group.
†$P<.05$.
‡$P<.01$.

With the exception of 2 voxels (1 in the cerebellum [Table 5], and 1 in the lentiform nucleus [Table 6]), no significant associations were detected for the controls. We did not detect positive associations in any of the analyses, neither in the AD nor in the control group.

COMMENT

Consistent with the prediction of the CR hypothesis, we found that activities had a negative correlation with CBF in patients with AD when controlling for disease severity. This relationship was seen primarily in voxels located in the temporal but also in temporal-occipital-parietal association cortices, the areas in which CBF changes are typically noted in AD. This inverse association was still present when both education and IQ were included in the model. This indicates that there is a unique relationship between activities and CBF over and above the relationship of CBF to education and IQ.

A previous study noted an inverse association between educational attainment and CBF (controlling for disease severity) in parietal areas.[11] In our study, we observed a similar negative correlation between education and CBF, localizing to parietal, frontal, and temporal regions.

Another study found an inverse association between premorbid IQ and CBF in prefrontal, premotor, orbitofrontal, superior parietal, thalamic, and anterior cingulate areas.[13] In our study, similar results (in terms of directionality of the relationship between IQ and CBF) were obtained. Significant correlations included thalamic, temporal, parietal, frontal, and cingulate areas in our study.

The observed differences in localization between previous studies and the present one could derive from the different types of functional imaging modalities used (xenon and fluorodeoxyglucose in previous studies vs oxygen 15 here), different covariates reflecting disease severity used in the analysis, different denominators used for intensity normalization, or different measures of IQ. Most notable, however, is the different methods of analysis: both previous studies used a region-of-interest analysis when they examined the associations between education and CBF and IQ and CBF,[11,13] while we elected to use a voxelwise analysis. Because we were able to replicate the directionality and, to a certain extent, the localization of these earlier findings with a voxelwise analysis, the validity of these previous observations is strengthened.

We detected significant associations in different areas of the brain depending on whether education or IQ or activities were used in the analyses. At first approximation, this may suggest that different aspects of CR mediate clinical protection in an anatomically specific way: ie, patients with high educational attainment can be maintained at similar clinical severity status when the pathologic changes AD affect certain areas of the brain, while patients with high IQ or leisure activity scores can be maintained when other brain regions are affected. Nevertheless, it is also possible that different aspects of CR are not region-specific and that the locations reported in our analyses generally co-localize to the same extended

Table 5. Local Maxima With a Statistically Significant Inverse Association Between Cerebral Blood Flow and Activity Scores*

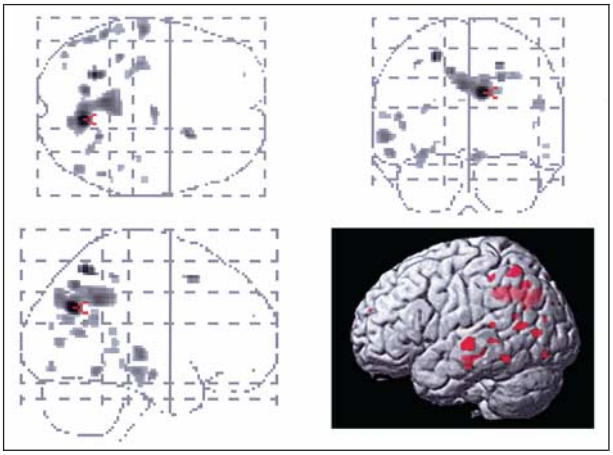
	Talairach Coordinates				
	x	y	z	*t* Values	Locations (Brodmann Area)
Activity score					
Alzheimer disease					
	10	−63	31	6.7†	Precuneus (7)
	−4	−45	35	5.7‡	Precuneus (31)
	0	−60	34	5.5‡	Precuneus (7)
	−24	−52	52	6.2‡	Precuneus (7)
	22	16	45	5.7‡	Superior frontal gyrus (8)
	−12	−60	44	5.6‡	Precuneus (7)
	−57	−19	−1	5.4‡	Superior temporal gyrus (21)
	22	−50	39	5.3§	Precuneus (7)
	32	−56	42	5.0§	Inferior parietal lobule (7)
	−53	−49	−9	5.3§	Inferior temporal gyrus (20)
	−32	−22	−11	5.3§	Parahippocampal gyrus
	−26	−30	−9	5.0§	Parahippocampal gyrus
	−38	−35	48	5.3§	Inferior parietal lobule (40)
	2	−14	−14	5.2§	Brainstem-mamillary body
	−50	−58	14	5.2§	Superior temporal gyrus (22)
	48	−67	24	5.1§	Middle temporal gyrus (39)
	51	−47	23	5.1§	Supramarginal gyrus (40)
	−46	−71	9	5.0§	Middle occipital gyrus (19)
	−30	−55	21	5.0§	Middle temporal gyrus (39)
	−38	−78	−6	4.9§	Inferior occipital gyrus (19)
	−57	−37	2	4.8§	Middle temporal gyrus (22)
	−32	−77	19	4.8§	Middle occipital gyrus (19)
	38	−24	−11	4.8§	Hippocampus
	−57	−38	13	4.8§	Superior temporal gyrus (22)
	46	−37	7	4.7§	Superior temporal gyrus (41)
	−24	55	19	4.7§	Middle frontal gyrus (10)
	55	−20	−12	4.6§	Middle temporal gyrus (21)
	−6	−63	25	4.6§	Precuneus (31)
	53	−43	−5	4.6§	Middle temporal gyrus (37)
Control					
	8	−47	−8	4.7§	Cerebellum

*The analyses were controlled for age and Mini-Mental State examination score. No positive associations were detected for either group.
†$P<.001$.
‡$P<.01$.
§$P<.05$.

association areas usually affected by AD. The combination of the limited number of subjects included in our analyses and our conservative approach for controlling for type I error might have limited our power to detect significant associations in the whole spectrum of affected areas of the brain. In addition, the locations reported in our analyses represent only local maxima of more extended areas of the brain (Figure 1). Maintaining intellectual and social engagement through participation in everyday activities seems to buffer healthy individuals against cognitive decline in later life.[43-45]

We recently reported the results of a longitudinal epidemiologic study in northern Manhattan, NY.[18] Thirteen leisure activities (intellectual, social, and physical in character) were assessed in 1772 healthy elderly subjects who were prospectively followed for up to 7 years. Even when multiple potentially confounding factors were controlled for, subjects with high leisure activity scores had 38% less risk of developing dementia. There are at least 2 other large prospective cohorts that have reported a protective effect for leisure[16] and cognitive activities[17] in relationship to incident dementia.

A limitation of the present study is that activities were assessed in patients with mild dementia and that the extent to which they participated in these activities might have been affected by the disease. Optimally, activities should have been recorded during presymptomatic periods. How-



Statistical parametric map and its 3-dimensional brain rendering representation depicting areas of significant (some $P<.001$, some $P<.01$, and some $P<.05$, as presented in Table 4) inverse correlations between cerebral blood flow and activities score in the Alzheimer group, controlling for age and Mini-Mental State Examination score.

Table 6. Local Maxima With a Statistically Significant Inverse Association Between Cerebral Blood Flow and Activity Scores*

	Talairach Coordinates				
	x	y	z	*t* Values	Locations (Brodmann Area)
Activity score					
Alzheimer disease					
	−42	−76	−1	6.9†	Inferior occipital gyrus (19)
	−46	−70	7	6.4†	Middle occipital gyrus (19)
	−50	−48	21	6.7†	Supramarginal gyrus (40)
	−50	−52	14	6.1†	Superior temporal gyrus (39)
	−59	−22	−4	5.1‡	Middle temporal gyrus (21)
	−38	−13	6	5.0‡	Insula
Control					
	32	−13	6	5.3‡	Lentiform nucleus

*The analyses were controlled for age, Mini-Mental State Examination score, education, and Nelson Adult Reading Test score. No positive associations were detected for either group.
†$P<.01$.
‡$P<.05$.

ever, as described in the "Results" section, our patients were at early stages of AD and the reported changes in their activities over the last 10 years were ostensibly negligible. We therefore used the recorded activity score as an estimate of lifestyle during the 10 years before study enrollment.

To further explore this potential bias, we repeated the analyses using reconstructed scores for the subjects who reported decreased time devoted to activities, adding in points for the activities they reported to exercise less over the last 10 years. The results for all models were essentially unchanged. We elected to use the contemporaneous activity score for the analyses because it is less prone to recollection bias. The fact that the activities information was corroborated by the informant also added to the face validity of the scores.

The activity scale items collected in this study reflected not only intellectual and social activities but also physical ones. Epidemiologic evidence that physical exercise may delay cognitive impairment is equivocal. While high levels of physical activity were associated with reduced risk of dementia in at least 4 prospective studies,[18,46-48] no effect of exercise on dementia and cognitive impairment risk was reported from other cohorts.[17,49] Additionally, there is basic research evidence that environmental enrichment in the form of voluntary wheel running is associated with enhanced neurogenesis in the adult mouse dentate gyrus.[50] It has also been shown that physical activity sustains cerebral blood flow[51] and may improve aerobic capacity and cerebral nutrient supply.[52,53] Therefore, although it is conceivable that physical activity may merely be a nonspecific marker of good health indirectly related to dementia (or not related to dementia at all), it is also possible that it has a direct physiologic association with brain disease.

Recent evidence indicates that certain areas of the brain retain the capability to generate new neurons into adulthood, not only in rodents[54] and primates[55] but also in humans.[56,57] Thus, it is possible that the stimulation provided by everyday intellectual and social activities facilitates the maintenance of general cognitive skills in a manner that is analogous to physical exercise for musculoskeletal and cardiovascular functions.[43] This reserve could be the result of a physiologic process involving increased synaptic density in the neocortical association cortex acquired by stimulation.[58]

This study does not indicate that more engagement in activities affords some kind of immunity to the neuropathologic aspect of the AD process. On the contrary, we assume that the pathologic changes in AD progress independently of life activities. The concept of CR was developed in an attempt to explain interindividual differences in the degree of pathologic changes in the brain necessary for the clinical expression of disease.[59] This has been confirmed in multiple studies, which have found that a significant proportion of clinically nondemented individuals manifest neuropathologic changes consistent with AD at autopsy.[60,61] More engagement in activities may supply a reserve that allows an individual to cope longer before AD is clinically expressed. Aspects of life experience, such as social, intellectual, and physical activities, could modify the paradigms used by the brain to mediate a task by making individuals more efficient or resilient in the face of pathologic changes in the brain or by recruitment of alternate networks.

The activity score may simply represent innate rather than acquired abilities. However, activities, education, and IQ seem to have a unique association to CBF, which supports the concept that aspects of life experience may modulate reserve. The hypothesized contribution of life experiences, styles, and activities to the ability to cope with the pathologic changes in AD suggests the possibility of interventions that might delay the onset of the clinical symptoms of the disease.

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