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Education-Associated Cortical Glucose Metabolism during Sustained Attention

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Abstract

Despite research suggesting that education may mitigate cognitive sequelae of neural injury, little is known about interactions between education and regional brain function. We examined whether educational experience is associated with relative glucose metabolism in brain regions that are important for sustained attention and learning. Fourteen healthy adults, with twelve to eighteen years of schooling, underwent positron emission tomography (PET) scanning with 18F-fluorodeoxyglucose (FDG) during an auditory continuous discrimination task. Years of education correlated positively with relative glucose metabolism in the lingual gyri (bilaterally), left posterior cingulate gyrus, and left precuneus. Previously, these structures have shown early impairment in dementia. Further investigation should explore whether metabolic changes in these regions contribute to the possible protective effect of education on cognition.

Keywords

Education; positron emission tomography; precuneus; lingual gyrus; posterior cingulate gyrus

Introduction

Recent data have suggested that education may mitigate neural damage and loss of functioning induced by brain injury from trauma, vascular accident and Alzheimer's dementia.[1,2,3] The possible mechanism by which such protection could be afforded, however, remains unclear. This knowledge might augment our understanding of neural resilience and ultimately help refine cognitive rehabilitation in the treatment of dementia and brain injury.

A review of the neuroimaging literature produces only one study that has investigated the correlation between an education-dependent variable (in this case, "cognitive reserve," calculated by combining years of education and IQ scores) and differences in task-related cerebral perfusion. This study found clusters of greater activation in the right inferior temporal gyrus and postcentral gyrus in young healthy adults with greater "cognitive reserve." However,

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the study utilized a visual (shape recognition) task whose difficulty was calibrated to individual task performance.[4] This approach may have varied the quality of cognitive effort between subjects. Such variations could be avoided by using a uniformly easy task, such as distinguishing between high- and low-pitched auditory stimuli.[5] To our knowledge, no prior research has examined the association between years of education and relative regional glucose metabolism in the brain during an auditory sustained-attention task.

Advanced education requires significant capacity for sustained attention and learning of complex language, mathematical, and visuospatial tasks. Functional imaging studies have identified association cortexes in the parietal (precuneus, posterior cingulate, inferior parietal cortex) and occipital lobes (lingual gyrus) as well as in the prefrontal cortex (dorsolateral and anterior cingulate/perigenual cortex) that are activated during these types of activities.[6,7,8, 9] Our goal was to evaluate whether educational experience is associated with regional metabolism in these areas of the brain during a sustained attention task.

Methods

Subjects

Participants were fourteen healthy adults recruited and studied as controls for an unrelated experiment.[10] Data was acquired from these subjects for the purposes of that experiment and subsequently analyzed for the current study. Inclusion criteria were right-handedness as defined by a score of greater than twenty on a modified Edinburgh Handedness Scale [11] and age 21 to 55 years. Exclusion criteria were: current or past Axis I diagnosis by Structured Clinical Interview for DSM IV (with the exception of nicotine dependence), gross structural abnormality on 1.5 Tesla double-echo brain MRI as read by a neuroradiologist, evidence of neurological or other systemic illness on physical exam or routine laboratory values, positive urine toxicology, and any history of head trauma, neurological, cardiovascular, pulmonary or systemic disease, or HIV seropositivity. Neither moderate use of caffeine (less than 600 mg of caffeine per day) or alcohol (less than fifteen drinks of liquor (1.5 oz) or the equivalent of beer (12 oz) or wine (5 oz) per week) nor occasional marijuana use (less than or equal to 1 marijuana cigarette/month and urine toxicology negative for THC) were exclusionary.

Four subjects were women, and ten were men. Their ages ranged from 22 to 49 years (mean 33 +/- 8.5 years), and their education levels ranged from 12 to 18 years (mean 15.6 +/- 1.8 years). Eight subjects had at least 16 years of education, corresponding to a complete college education (mean 16.9 +/- 0.93 years) and six did not (mean 13.8 +/- 1.2 years). Subjects completed the WAIS-R Vocabulary Test, a test of verbal function and the subtest of the WAIS-R that most correlates with general IQ.[12] Average scores on the Vocabulary Test ranged from 7 to 19 (mean 12.4 +/- 3.68), though data was unavailable for two subjects due to clerical error. All participants provided written informed consent and were financially compensated for their time.

Scanning Procedures

For PET studies, a catheter was inserted into the antecubital vein for infusing FDG, and the participant was positioned in the scanner gantry, and custom-fitted with a thermoplastic facemask (Stryker Systems, Annapolis, MD) to minimize head motion. A 20-min ^{68}Ge transmission scan provided data for attenuation correction. The subject was then removed from the scanner and performed a continuous performance task (CPT) (version 2.26, Sunrise Systems; Pembroke, MA). The task required discrimination of a target tone (higher pitch) from a sequence (inter-stimulus interval = 2 sec) of non-target tones (lower pitch). Pressing the "x" on the computer keyboard signified hearing a target tone. Ambient sounds were masked with "pink" noise (70 dB) during FDG uptake. With the CPT underway, FDG ($< 5 \text{ mCi}$, $< 185 \text{ MBq}$)

was administered intravenously. Thirty minutes later, the CPT was stopped, and the subject was repositioned in the scanner. CPT error rates were calculated for the first 450 responses after injection. PET scans were acquired with a Siemens ECAT EXACT HR +, with a 15.5-cm field of view at the NIDA Brain Imaging Center. The average transverse resolutions (full width half maximum (FWHM)) of the scanner at 1 and 10 cm from the center of the field of view, measured in 3D mode and determined using a fluorine-18 line source and a ramp filter (with a 0.5 cutoff frequency) were 4.66 mm and 5.45 mm, respectively. The emission scan was acquired in 3D mode as six dynamic frames for 5 minutes each. The subject was then removed from the tomograph and instructed to void to reduce the radiation dose to the bladder.[13] The Institutional Review Boards of NIDA and Beth Israel Medical Center approved all research procedures.

Data Analyses

Each frame was reconstructed by using the vector processor of the scanner in 3D mode by filtered back-projection (128 matrix size and zoom factor of 2.75). Scatter correction, decay correction, and attenuation correction were applied by using a Hann filter with a 0.5 cutoff frequency. The reconstructed dynamic frames were summed after they were viewed in a cine viewer to verify that there were no motion artifacts. If evidence of motion was detected in any of the frames, the frames were excluded from summing.

PET images were analyzed using statistical parametric mapping (SPM99, Wellcome Dept. of Cognitive Neurology, University College London). The decay-corrected PET images were converted to Analyze 7.5 volume image format and then spatially normalized into the Montreal Neurological Institute coordinate system (i.e., MNI space). The spatially transformed images contained isotropic 2-mm voxels and were smoothed with an 8×8×8 Gaussian filter.

Seven brain regions, selected because they were previously demonstrated to be selectively activated during attention and learning of complex language, mathematical, and visuospatial tasks, were sampled in both hemispheres: precuneus (BA7), lingual gyrus (BA19), inferior parietal cortex (BA40), middle anterior cingulate gyrus (BA24), perigenual anterior cingulate gyrus (BA24/32/33), dorsolateral prefrontal cortex (BA10), and posterior cingulate (BA24). [6,7,8,9] Fourteen volumes of interest (VOI) were created, using MEDx 3.42 image processing program (Sensor Systems, Sterling, VA). Each individual VOI was traced on a T1-weighted MRI image normalized to the same stereotaxic space as the PET images and with the same voxel dimensions. The 3-D contour of a particular structure was derived from the series of 2-D graphics by outlining its borders and saved as a VOI.

The smoothed normalized images were proportionally scaled to the global brain value to yield relative rates of rCMRglc. The voxel-wise threshold for inclusions in clusters was set at $P < .005$, and clusters of contiguous voxels (with a minimum spatial extent of 10 voxels) were considered significant at $P < .05$, corrected for search volume. For all analyses, age was treated as a nuisance covariate. Relationships between relative rCMRglc and education, rCMRglc and CPT error rate, and rCMRglc and WAIS-R Vocabulary score were tested using covariate analysis. Statistical significance of the effect of each covariate was assessed within the 14 pre-selected VOIs (seven bilateral regions). Separate SPM analyses were performed for each covariate, yielding SPM (t)s. The small volume correction within each VOI was applied. A VOI was considered to show a significant covariate effect if it contained a cluster with $P < .05$ for spatial extent (corrected). In each VOI that showed significant covariance using these criteria, the probability associated with the peak voxel height (corrected for search volume) was also noted.

Results

A positive correlation was found at the left lingual gyrus ($p=0.024$; 84 voxels; maximal activation at $-4x, -82y, 4z$; $z\text{-score}=2.97$), right lingual gyrus ($p=0.002$; 213 voxels; maximal activation at $8x, -62y, 2z$; $z\text{-score}=3.49$), left posterior cingulate ($p=0.025$; 69 voxels; maximal activation at $-2x, -34y, 32z$; $z\text{-score}=3.29$), and left precuneus ($p=0.015$; 112 voxels; maximal activation at $0x, -54y, 54z$; $z\text{-score}=3.53$). See Figures 1-4. A positive correlation that approached statistical significance was also found at the right precuneus ($p=0.056$; 57 voxels; maximal activation at $2x, -54y, 56z$; $z\text{-score}=3.59$). No statistically significant relationship between education and relative activity was found in the inferior parietal, anterior cingulate, or dorsolateral prefrontal cortices. No significant correlation between relative activity and either the WAIS-R Vocabulary Test or CPT error rate in any of the selected VOIs was found.

No significant relationship by Pearson's or rank correlation coefficient tests was present between WAIS-R Vocabulary Test performance and years of education, between WAIS-R Vocabulary Test performance and CPT error rate, or between years of education and CPT error rate.

Discussion

This study sought to assess whether level of education is related to regional brain metabolism during a sustained attention task. PET scans of individuals with more years of education demonstrated greater relative activity in the lingual gyrus, precuneus and left posterior cingulate. Because CPT error rate did not correlate with years of education or with relative regional activity, the present results are unlikely to be due to performance inconsistencies alone. Likewise, it is less probable that the associations identified are merely general intelligence effects because WAIS-R Vocabulary scores did not correlate with years of education or with relative regional activity.

Supratentorial cortical neurodevelopment appears to progress in a posterior to anterior direction, with the occipital cortex acquiring myelin prior to the frontal cortex.[14] The medial posterior parietal and occipital cortexes, such as the precuneus, develop early and should be fully formed by the ages of our subjects.[15] By identifying an association between education, an environmental variable, and regional metabolic activity in these areas, the present data are consistent with the notion of experience-driven regional neuroplasticity continuing to modulate brain function in the healthy adult brain. However, our study design cannot formally support a causal relationship between educational experience and the observed cerebral metabolic activity. Furthermore, the precise significance of activity on positron emission tomography in this context cannot be ascertained from the current data (e.g., whether this represents intrinsic synaptic rewiring in this area or simply increased recruitment of existing circuitry).

The observed areas of education-associated cerebral metabolism in our analysis all subserve advanced visual language processing. Both the precuneus and lingual gyrus respond to word as opposed to non-word visual stimuli, a response that is delayed but persistent when the presented stimuli are rotated.[16] The left precuneus shows increased activation when reading high- rather than low-frequency Chinese characters, and the lingual cortex has the reverse preference.[17] It is reasonable to posit that this augmented activity of the lingual gyrus, precuneus, and posterior cingulate in concert may be associated with the particular linguistic demands of advanced education. Additionally, the auditory nature of the continuous performance task may have contributed to highlight these regions.

Of great interest, the current results may help begin to provide a hypothetical rationale for education's possible protective effect on cognition. The precuneus and neighboring posterior cingulate cortex occupy a vulnerable site in the medial parietal lobe on the border of the anterior

and posterior cerebral arterial territory. They are tonically active during baseline wakefulness, and their metabolism correlates directly and dramatically with level of consciousness.[18] They suffer significant decline in functioning with diminished consciousness and coma [19] and early loss of activity in Alzheimer's dementia.[20] Both the precuneus and lingual gyrus (medial occipitotemporal gyrus) suffer age-related loss of volume bilaterally in non-demented adults with Down's syndrome, a population prone to Alzheimer's disease.[21] Presumptively, more robust neuronal circuits in these structures may prove advantageous in the face of Alzheimer's dementia or similar insult.

The lack of education-associated prefrontal changes was unexpected. Mathematical tasks recruit frontal and prefrontal regions in addition to the precuneus and left cingulate cortex.[9] Furthermore, both the dorsolateral prefrontal cortex and precuneus are involved in pitch discrimination tasks.[22,23] The lack of anterior findings could suggest that advanced educational experience may be associated more robustly with modifications in analysis of incoming visual and linguistic data than with executive processing. Alternatively, perhaps those with more mathematically oriented educational experience do have altered prefrontal activation, an effect that could have been masked by the small and heterogeneous sample population. These of course remain speculative, and additional studies with both functional imaging and neuropsychological testing data to address such possibilities are needed.

There are several limitations to this study. The small sample size and consequent narrow range of subjects' years of education, for instance, posed a constraint on the analysis. However, the fact that data analysis nonetheless revealed statistically significant and bilateral findings across this narrow educational range we feel strengthens the results. Additionally, the WAIS-R Vocabulary Test data may not have been a sufficiently sensitive measurement of intelligence in such a small number of subjects. However, this test is frequently utilized as a test of general intelligence, and we included it to help rule out the possibility that years of education was not a mere surrogate variable for preexisting, innate intelligence that might predispose a subject to advance farther in schooling.[24] Importantly, we cannot eliminate the possibility that our data are confounded by untested variables, such as nutritional status, socioeconomic status, or exercise, which might relate to both education and relative regional brain metabolism. Future work is needed to more thoroughly examine the effects of such confounding variables with a number of instruments and on a greater number of subjects.

Conclusion

Despite its limitations, this is the first study known to the authors, which has demonstrated education-associated metabolic activity in this constellation of structures (lingual gyri, precuneus, and posterior cingulate gyrus). We believe larger investigations are warranted to validate these initial findings in a broader population and to continue to evaluate the understudied relationship between education and regional cerebral metabolism.

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References

1. Dufouil C, Alperovitch A, Tzourio C. Influence of education on the relationship between white matter lesions and cognition. *Neurology* 2003;60:831–6. [PubMed: 12629242]

2. Kesler SR, Adams HF, Blasey CM, Bigler ED. Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Appl Neuropsychol* 2003;10:153–62. [PubMed: 12890641]
3. Stern Y, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol* 1992;32:371–5. [PubMed: 1416806]
4. Scarmeas N, Zarahn E, Anderson KE, Hilton J, Flynn J, Van Heertum RL, et al. Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects. *Neuroimage* 2003;19:215–27.
5. Seidman L, Breiter H, Goodman J, Goldstein J, Woodruff P, O'Craven K, et al. A functional magnetic resonance imaging study of auditory vigilance with low and high information processing demands. *Neuropsychol* 1998;12:505–518.
6. Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ. Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. *Brain* 1997;120:1779–1791. [PubMed: 9365370]
7. Johannsen P, Jakobsen J, Bruhn P, Gjedde A. Cortical responses to sustained and divided attention in Alzheimer's disease. *Neuroimage* 1999;10:269–81. [PubMed: 10458942]
8. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative. *Cereb Cortex* 1992;2:435–443. [PubMed: 1477524]
9. Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkn S. Sources of mathematical thinking: behavioral and brain-imaging evidence. *Science* 1999;284:970–4. [PubMed: 10320379]
10. Galynker I, Matochik JA, Gertmenian-King E, Cohen L, Weaver C, Kimes AS, et al. Regional brain metabolism and negative affect in opiate abusers receiving or removed from long-term methadone maintenance. 2004Submitted
11. McKeever WF, Seitz KS, Krusch AJ, Van Eys PL. On language laterality in normal dextrals and sinistrals: results from the bilateral object naming latency task. *Neuropsychologia* 1995;33:1627–1635. [PubMed: 8745120]
12. Wechsler, D. Wechsler Adult Intelligence Scale – Revised Manual. New York: Harcourt, Brace, Janovich Publishers; 1982.
13. Mejia AA, Nakamura T, Itoh M, Hatazawa J, Ishiwata K, Ido T, et al. Absorbed dose estimates in positron emission tomography studies based on the administration of 18F-labeled radiopharmaceuticals. *J Radiat Res* 1991;32:243–261. [PubMed: 1838773]
14. Barkovich AJ, Kjos BO, Jackson DE, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Neuroradiology* 1988;166:173–180.
15. Chugani H, Phelps M, Mazziotta J. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22:487–497. [PubMed: 3501693]
16. Bellgowan PS, Saad ZS, Bandettini PA. Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width. *Proc Natl Acad Sci USA* 2003;100:1415–9. [PubMed: 12552093]
17. Kuo WJ, Yeh TC, Lee CY, Wu YT, Chou CC, Ho LT, et al. Frequency effects of Chinese character processing in the brain: an event-related fMRI study. *Neuroimage* 2003;18:720–30. [PubMed: 12667849]
18. Raichle M, MacLeod A, Snyder A, Powers W, Gusnard D, Shulman G. A default mode of brain function. *Proc Natl Acad Sci USA* 2001;98:676–82. [PubMed: 11209064]
19. Laureys S, Antoine S, Boly M, Elincx S, Faymonville ME, Berre J, et al. Brain function in the vegetative state. *Acta Neurol Belg* 2002;102:177–85. [PubMed: 12534245]
20. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997;42:85–94. [PubMed: 9225689]
21. Teipel SJ, Alexander GE, Schapiro MB, Moller HJ, Rapoport SI, Hampel H. Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. *Brain* 2004;127:811–24. [PubMed: 14985261]
22. Platel H, Price C, Baron JC, Wise R, Lambert J, Frackowiak RS, et al. The structural components of music perception, a functional anatomical study. *Brain* 1997;120:229–43. [PubMed: 9117371]

23. Ohnishi T, Matsuda H, Asada T, Aruga M, Hirakata M, Nishikawa M, et al. Functional anatomy of musical perception in musicians. *Cerebl Cortex* 2001;11:754–60.
24. Kaufman AS, McLean JE, Reynolds CR. Sex, race, residence, region, and education differences on the 11 WAIS-R subtests. *J Clin Psychol* 1988;44:231–48. [PubMed: 3360941]

Figure 1. Locations of positive covariation (small volume correction analysis) between relative rCMRglc during auditory discrimination task and years of education in healthy subjects (n = 14).

Figure 2.
Relative rCMRglc during auditory discrimination task as a function of years of education in healthy subjects at the left posterior cingulate (n=14).

Figure 3. Relative rCMRglc during auditory discrimination task as a function of years of education in healthy subjects at the right lingual gyrus (n=14).

Figure 4. Relative rCMRglc during auditory discrimination task as a function of years of education in healthy subjects at the left precuneus. (n=14).