REVIEW

A Review of Functional Brain Imaging Correlates of Successful Cognitive Aging

Lisa T. Eyler, Abdullah Sherzai, Allison R. Kaup, and Dilip V. Jeste

Preserved cognitive performance is a key feature of successful aging. Several theoretical models have been proposed to explain the putative underlying relationship between brain function and performance. We aimed to review imaging studies of the association between brain functional response and cognitive performance among healthy younger and older adults to understand the neural correlates of successful cognitive aging. MEDLINE-indexed articles published between January 1989 and December 2009 and bibliographies of these articles and related reviews were searched. Studies that measured brain function with functional magnetic resonance imaging or positron emission tomography, evaluated cognitive performance, analyzed how cognitive performance related to brain response, and studied healthy older individuals were included. Eighty of 550 articles met these criteria. Seventy percent of the studies reported some brain regions in which greater activation related to better cognitive performance among older participants. This association was not universal, however, and was seen mainly in frontal cortex brain response and seemed to be more common among older compared with younger individuals. This review supports the notion of compensatory increases in brain activity in old age resulting in better cognitive performance, as suggested by hemispheric asymmetry reduction and posterior–anterior shift models of functional brain aging. However, a simple model of bigger structure → greater brain response → better cognitive performance might not be accurate. Suggestions for future research are discussed.

Key Words: Aging, brain imaging, cognition, frontal cortex, functional magnetic resonance imaging (fMRI), positron emission tomography (PET)

A great challenge for future society will be to better understand the aging process. As the proportion of individuals over age 65 grows, it is of utmost socioeconomic importance to promote functional independence and quality of life in this group. Cognitive health has consistently been cited by seniors as important for quality of life (1) and is widely recognized by researchers as an important contributor to late life functioning (2–4). Thus, a key element in dealing with the "graying of the world" must be to discover ways to optimize cognitive performance in old age.

Cognitive performance in most domains declines with age, particularly processes such as psychomotor speed; however, some abilities might remain stable or even improve up to a certain age, such as vocabulary (5). Importantly, there is large heterogeneity in cognitive changes that occur with aging (6). Some seniors are exceptional in their cognitive performance, and understanding this aspect of cognitive aging (as opposed to focusing on pathological change or normal declines) is likely to guide the search for ways to enhance cognitive functioning in aging (3).

Brain health is an important determinant of cognitive health, so a fuller understanding of neural aging, especially those aspects that most influence cognition, is necessary. Much is already known about structural brain changes due to age and age-related diseases (7) and how these relate to cognitive performance (8). We observed, in a comprehensive review of the literature focusing on structural correlates of cognitive performance in healthy elders, that most studies find a positive relationship between regional brain size and cognitive performance (9).

Brain structural integrity, however, is only one neural factor influencing individual differences in cognitive function among older people. Studies of brain function using techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed reliable changes in the level and pattern of brain activity with age. Older age has been associated with lower blood flow and metabolism at rest, particularly in frontal cortex (10). Reduced regional brain response to challenge tasks among older compared with younger participants has also been seen (11). Notably, however, greater regional brain response in older participants also is commonly observed (11). In some instances, pattern of brain response is qualitatively different, for example, when "overactivation" occurs in a homologous region in the opposite hemisphere from the region typically responsive in the young group and is less lateralized, referred to as Hemispheric Asymmetry Reduction in OLDer adults (HAROLD) (12). In other cases, brain response in posterior regions has been found to be lower in older adults, whereas anterior regions show greater response than in younger individuals. This relative shift from posterior to anterior involvement has been termed the Posterior–Anterior Shift with Aging (PASA) (11).

An unresolved issue is how these age-related changes in brain responsiveness and altered patterns (e.g., HAROLD or PASA) are associated with cognitive differences between older individuals and with rates of cognitive decline with aging. Age-related alterations in brain function might be associated with poorer cognitive performance, as seen most dramatically in the case of decreased regional metabolism associated with steep cognitive declines in Alzheimer's dementia (13). Interestingly, however, there is also evidence that the degree to which older individuals manifest some age-related patterns of brain activity might be associated with better cognitive performance (i.e., compensation, as discussed in the brain reserve [14] and scaffold [15] models of cognitive aging). Such findings are in contrast to the idea that alterations of neural function reflect inefficient processing (i.e., de-differentiation) (16).

The purpose of this review was to comprehensively review studies of the association between cognitive performance and brain function among healthy older individuals to weigh evidence in support of age-related compensatory versus de-differentiated

From the Sam and Rose Stein Institute for Research on Aging (LTE, DVJ); Department of Psychiatry (LTE, ARK, DVJ), University of California San Diego; Mental Illness Research, Education, and Clinical Center (LTE), VA San Diego Healthcare System; San Diego Joint Doctoral Program in Clinical Psychology (ARK), San Diego State University/University of California, San Diego; and the Department of Neurology (AS), Loma Linda University, Loma Linda, California.

Address correspondence to Lisa T. Eyler, Ph.D., University of California San Diego, Mail Code 9151B, 9500 Gilman Drive, La Jolla, CA 92093; E-mail: lteyler@ucsd.edu.

Received Apr 15, 2010; revised Dec 4, 2010; accepted Dec 13, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.12.032

brain responses, examine factors related to these findings, and evaluate their specificity to old age. Previous reviews of functional imaging changes with age (11,17) have summarized a subset of findings covered in the present review, but none has focused specifically on correlations between brain function and cognitive performance.

Methods and Materials

To retrieve studies for this review, we surveyed MEDLINE citations (January 1989–December 2009, human studies, in English) with the National Library of Medicine PubMed online search engine with the following search string: ("functional MRI" OR "fMRI" OR "functional magnetic resonance imaging" OR "PET" OR "positron emission tomography" OR "cerebral blood flow") AND (brain OR cognition OR cognitive OR cerebral) AND (age[Title] OR aging[Title] OR aging[Title] OR old[Title] OR elderly[Title]) NOT (dementia[Title] OR Alzheimer's[Title] OR psychiatric[Title] OR disorder[Title] OR disease[Title] OR impair*[Title]). This search revealed 539 articles of potential interest. References cited in these articles were also examined, and we found 11 additional relevant publications.

Inclusion Criteria

We applied several selection criteria. To be included in the review, studies had to: 1) use fMRI or PET methodology to examine neural functioning, 2) evaluate cognitive performance either on a task given during imaging or on a measure administered on a separate occasion, 3) report results of an analysis examining how differences among individuals in cognitive performance related to differences in brain response, and 4) include at least one group of healthy elderly individuals (mean age $>$ 60 years).

Review Process

We found 80 reports that met review criteria (18–97). Flow of information through different stages of the systematic review is shown in Figure S1 in Supplement 1.

Each study was examined by two authors (LTE, AS, or AK), and the following information was extracted: numbers and characteristics of participants, definition of "healthy," neuroimaging method, scanning paradigm, and brain regions examined. We also noted whether participants overlapped between samples in the review. We summarized the relationship of age to functional brain imaging measures, on the basis of study results, to provide a context for understanding brain-cognition relationships. We then extracted the measures of cognitive performance that were used and summarized associations between cognitive performance and brain functioning. We noted the direction of association and whether this reflected greater response among those with successful versus normal cognitive performance (e.g., positive correlations for accuracy and negative correlations for reaction time both imply that better cognitive performers have greater brain response). When possible, we summarized correlations separately for younger and older groups. We were not able to use a meta-analytic approach such as activation likelihood estimation (98), because few studies conducted a whole-brain correlation analysis and there were large between-study differences in tasks and cognitive measures.

Results

Characteristics of Reviewed Studies

Study characteristics and results for the 80 reviewed articles are presented chronologically in Table S1 in Supplement 1. There were two reports from the same longitudinal study (64,80); two studies examined cognitive change longitudinally and brain response only once (54,78); all other investigations were cross sectional. Among cross sectional studies, six (27,41,45,47,72,73) included only older participants, one examined a large cohort ranging in age from 20 to 87 (21), and the rest (n = 73) compared younger adults to at least one group of older individuals. One study (42) reported partial overlap in participants with another study (36).

Summary statistics for the reviewed studies are given in Table 1. The review included more than twice as many studies using fMRI than PET, and sample sizes were typical of many functional neuroimaging investigations. A large majority of reports employed medical, neurological, and psychiatric screening criteria to assure a

Table 1. Summary of Study Characteristics for Reports in Review

Study Characteristic Sample Characteristic	Summary			
	Young Sample		Old Sample	
	Median	Range	Median	Range
Number of Participants	12	0–40	16	6–69
Gender Ratio (men/women)	1 (mean: 1.3)	.1–9	1 (mean: 1.0)	.1–3
Mean Age (yrs)	24	19.5–33.4	69.2	59–81.5
Minimum Age (yrs)	20	18–30	62	50–73
Maximum Age (yrs)	29	25–49	78	63–93
Mean Education (yrs)	15.8	12.8–18.2	15.7	10.2–19.3
Image Modality (no. of studies)	55 fMRI, 25 PET			
Exclusion Criteria (no. of studies)[a]	71 neurological, 64 psychiatric, 56 medical, 54 cognitive, 38 medications, 19 radiological abnormalities			
Challenge Task (no. of studies)[a]	32 episodic memory (phase: 18 encoding, 23 retrieval [method: 4 recall, 20 recognition]; stimuli: 20 verbal, 8 figural, 4 faces, 3 abstract), 15 working memory (stimuli: 9 verbal, 3 spatial, 2 facial, 1 object, 1 auditory), 6 rest, 5 inhibitory, 5 language, 5 nondeclarative memory, 3 emotion perception, 3 visual discrimination, 2 visual search, 2 visual attention, 2 motor, 1 reaction time			
Brain Regions Examined (no. of studies)[a]	1 whole brain (single value), 54 voxel-wise with whole brain coverage, 38 region of interest			
Measure of Cognitive Performance (no. of studies)[a]	59 accuracy, 36 reaction time, 4 composite of accuracy and reaction time; 65 on the basis of scanner task performance, 16 on the basis of tasks given outside of scanner			

fMRI, functional magnetic resonance imaging; PET, positron emission tomography.
[a]Note that the number of studies does not always add up to 80 across the categories, because a study could be counted in more than one category.