Neuropsychological "Systems Efficiency" and Positron Emission Tomography

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Positron emission tomography (PET) has dramatically improved our ability to examine the functioning of the living brain. PET studies of neural pathways of the major sensory modalities—auditory, visual, somatosensory—have confirmed many traditional neuropsychological concepts, such as cross-lateral representation and regional functioning to particular primary sensory cortical areas. Other PET studies have used radioisotopes to examine relationships between radiopharmaceutical agents and neurobehavioral functioning in both normal and neuropathological states. In some areas, PET methodology requires further refinement. For example, effort should be made to develop the technology to do multiple scans within a short time frame; statistical procedures to examine relationships between neuropsychological tasks and the activity or presence of radiopharmaceutical agents in multiple sites; adequate controls for experimental error; and activation paradigms controlling the nonspecific effects of simple arousal. PET activation models of cognition suggest that a "systems efficiency" approach to assessing neuropsychological test performance involving both serial and parallel processing would be useful. These developments will improve empirical methodology and our understanding of brain–behavior relationships.

Rapid expansion in the number of techniques available to dynamically image the brain has occurred over the last decade. One technique, positron emission tomography (PET), was developed by researchers in the fields of nuclear physics, organic chemistry, and physiological medicine. In PET, a small dose of a positron-labeled material is injected into the bloodstream. Detectors are used to determine the rate of uptake and decay of the positron-containing agent in the brain.

One material commonly used for PET studies is [^{18}F]2-fluoro-2-deoxyglucose (FDG); it is metabolized in the pathway that breaks glucose down into water and carbon dioxide. Using the model developed by Sokoloff,[1,2] investigators can calculate glucose metabolic rates in regions of the brain from PET measurements and assays of the peripheral arterial levels of FDG and glucose. Computer reconstruction yields the relative rates of FDG uptake and retention. The data are displayed as a brain image, much like computerized tomography (CT) scans or magnetic resonance imaging (MRI).

Unfortunately, the spatial resolution in PET does not approach resolution obtained with CT or MRI because of limitations of machine design and more fundamentally

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because of the decay characteristics of positron emitters. Most studies have been done using machines with a resolution capability of 8 mm to 15 mm, a range that severely limits the ability to perceive cortical and subcortical detail. Nevertheless, PET provides a way to investigate regional brain–behavior relationships in normal and pathological conditions.[3-8] In addition, PET studies of changes in metabolic activity in different brain regions provide new insights on how changes in metabolic activity in the brain are organized into a neural network in response to cognitive demands. They also shed light on how communication among these neural networks, which represent diverse neuropsychological functions, is maintained.[9-11]

It is important to recognize that PET procedures provide only a "snapshot" of regional brain glucose metabolic activity during a discrete time period. Acquisition of the "snapshot" involves a relatively long exposure time because it must cover the period of active uptake of FDG from blood to brain. Moreover, the "exposure" is not linear over time—it decays in logarithmic fashion. Therefore, if brain activity itself varies during the time of FDG accumulation, the image obtained may also vary.

This article provides an overview of the studies to date that have used regional uptake of FDG and other radiopharmaceutical agents to investigate brain functioning in normal and demented subjects. We propose a "systems efficiency" model of the theoretical foundation of neuropsychological test performance based on current cognitive-challenge PET procedures. Methodological problems associated with localization of brain function are addressed, and finally, suggestions are made for future directions in the application of PET technology.

AUDITORY PATHWAYS

In most PET studies of the auditory pathways, verbal stimuli are presented to normal resting subjects who are under conditions of reduced sensory input. Stimuli usually consist of both meaningful and nonmeaningful auditory material. *Activation* is defined as changes in brain activity, which are measured by rates of FDG uptake. Comparisons are made between measurements taken from relatively inactive control areas and measurements taken from the hypothesized centers of activity along the auditory pathways. Areas of increased activity are interpreted as resulting from stimulation of pathways and sites important in the processing of verbal material. Areas of decreased activity are thought to represent pathological states in which appropriate neuronal nets cannot be activated. Only a few studies have concentrated on the temporal patterns of such responses or on the relationship of activity levels between multiple areas of the brain. However, they have provided some basic insights into cortical responses to auditory stimulation.

In one of the first PET studies of auditory pathways, by Alavi et al.,[12] normal subjects listened to tape-recorded factual stories. To control subjects' motivation, subjects received remuneration based on the accuracy of their recall, which was assessed after the scan was completed. Information was presented to the right or the left ear through earphones with the opposite ear plugged, and subjects were blindfolded to reduce extraneous activation through visual pathways.

Seven subjects were stimulated with a meaningful story; six showed increased glucose metabolism in the right temporal cortex, independent of which ear received the stimuli. In the same experiment, subjects also listened to a story recorded in Hungarian, a language none of them understood. The subjects' attention was maintained by requiring them to respond each time they heard a target word that occurred at random throughout the discourse. Subjects again showed increased activity in the right temporal lobe, regardless of whether the right or the left ear was stimulated. The investigators interpreted these results as consistent with evidence indicating that the right hemisphere contributes to the processing of linguistic information.[13] Citing studies of dichotic listening,[14,15] Alavi et al.[12] suggested that their subjects may have adopted complex strategies involving functional interactions within the auditory pathway to produce right hemisphere activation. Their report of unexpected right-hemisphere activation of the auditory cortex provoked great interest among researchers.

In contrast to the study by Alavi et al.,[12] Greenberg et al.[16] found that subjects presented with factual stories monaurally had increased FDG uptake in the auditory cortex contralateral to the stimulated ear. These results are more consistent with traditional functional models of the auditory system derived from neurophysiological studies in animals[17] and humans.[18]

Other research indicated that as the complexity of the material increased, FDG uptake extended beyond the areas normally associated with the primary auditory system. When subjects listened to a tape recording monaurally or binaurally, activation was detected in the frontal lobes as well as in the temporal lobes.[19] This additional activation may have occurred as attention and short-term memory became engaged.

Auditory input also activates subcortical areas. Mazziotta et al.[20] have shown that bilateral increases in FDG uptake occur in the thalamus when monaural verbal material is presented.

In another series of experiments, Mazziotta et al.[21] demonstrated significant increases in metabolic rate in multi-

ple brain areas during monaural presentation of a tape-recorded story compared with the resting state. Increases were seen in the left frontal cortex, left thalamus, bilateral posterior cortex, and transverse temporal cortex. Interestingly, the left hemisphere showed greater increases in FDG uptake in response to verbally meaningful material than did the right hemisphere, regardless of whether the right or the left ear was stimulated. By contrast, greater metabolic asymmetry in favor of the right hemisphere was noted when subjects were stimulated with items from the Timbre Test,[22] regardless of the ear receiving the stimulation. When the Tonal Memory Test, which has more complex musical stimuli, was presented, the site of cortical activation depended on the musical sophistication of the subject.[22] Subjects with musical training demonstrated greater metabolic activity in the left posterior superior temporal cortex than in the analogous area of the right hemisphere. Subjects without musical training exhibited signs of increased metabolism in the right hemisphere, particularly in the frontal and parietotemporal regions. Thus, Mazziotta et al.[21] suggested that auditory hemispheric specialization can be varied not only by the stimulus parameters but also by the individual's cognitive strategy.

As a whole, these findings illustrate the importance of controlling not only for the complexity of the auditory stimuli but also for differences between individual subjects—in these cases, prior musical training and cognitive strategies for solving the problems presented—when designing research protocols. They also highlight the need to further explore the role of auditory attentional networks, which are thought to be located in the frontal regions or right hemisphere of the brain.

VISUAL PATHWAYS

Focal increases in FDG uptake in the striate cortex contralateral to the stimulated visual field have been demonstrated in normal volunteers.[12,16] Subjects were required to fix their gaze while one-half of the visual field was darkened and the other half was presented with patterns of stroboscopically illuminated, black and white lines moving at varying orientations. Subsequently, abstract colors were also presented to one-half of the visual field. The use of a diverse range of intensities and a wide variety of visual stimuli made it difficult to interpret the exact relationship between specific visual-stimulus components and metabolic activity in the visual cortex. In spite of these methodological problems, hemifield visual stimulation resulted, without exception, in a contralateral increase in FDG uptake in the calcarine area.

In subsequent studies, Kushner et al.[23,24] used a black-and-white pattern to examine the effect of stimulating different retinal areas on regional FDG uptake in the human visual cortex. Their results supported the accepted view that central vision activates the postero-medial striate cortex. An absence of significant increases in FDG uptake in the anterior striate cortex when peripheral vision was stimulated may have reflected limitations of the activation procedure or limitations in resolution of the imaging procedure. Visual stimulation with patterns induced significant changes confined to the right hemisphere. These findings suggested that some of the organization of the visual pathways beyond the occipital region of the brain is independent of the spatial location of the visual stimulus.[25]

Perhaps the most intriguing findings were reported by Phelps et al.,[26,27] who examined patterns of FDG uptake in response to increasingly complex visual stimuli. Their experimental conditions ranged from eyes-closed to stimulation with white light to an alternating black-and-white checkerboard pattern and a complex visual scene. In normal subjects, monocular stimulation produced the expected differences between right-side and left-side uptake of FDG, and activity in the associative visual cortex increased as the complexity of the stimuli increased. In patients with lesions of the visual cortex, increased lesion severity was associated with progressively lower metabolic activity at the retinal, geniculate, and cortical levels. These findings indicate the active participation of geographically dispersed areas of the brain, even when a single modality of stimulation is employed.

SOMATOSENSORY PATHWAYS

When Greenberg et al.[16] investigated the effects of tactile stimulation on FDG uptake, they failed to find significant increases in postcentral cortical activity contralateral to the site of tactile stimulation. Moreover, they reported that both stimulated and unstimulated subjects showed considerable overlap in the magnitude of hemispheric asymmetry in FDG uptake in the postcentral gyrus. This asymmetry suggests that large changes in cortical activity occur in response to unspecified stimuli and emphasizes the need to develop standardized techniques to obtain homogeneous estimates of baseline states in control and experimental subjects.

Alavi et al.[12] reported that sensory-deprived subjects who were stimulated with painless brush strokes to the hand showed greater contralateral than ipsilateral postcentral cortical activity. This effect was not as prominent as the response elicited by either visual or auditory stimuli, suggesting that somatosensory functions are represented more precisely in the cortex than are the other

sensory modalities. Although the activated area encompassed a larger region than the researchers had predicted for cortical representation of the finger and hand, it did not obtrude into areas corresponding to the cortical representation of the face and lips. These findings reinforce the concept of high specificity of cortical representation of somatosensory pathways.

Clark et al.[28] studied the correlation of regional cortical glucose metabolism to mild electrical shocks applied to the right forearm of their subjects. The pattern of significant correlations at different levels of the brain was consistent with the distribution of ipsilateral and contralateral sensory pathways and their projections to the cortex. In particular, they found a high degree of association among regions of interest in the frontal areas of the brain in normal subjects. They also reported correlations between left-sided and anterior bilateral regions of the brain that occurred significantly more often than expected by chance. They stated that analysis of the variance-covariance matrices allowed them to avoid several potential sources of error, including methods of standardizing glucose metabolism rates, violations of statistical assumptions, and the partial-volume effect.

The organization of the somatosensory cortex has also been studied using tactile identification (sorting tiles), a graphesthesia test (detecting numbers traced on the palm of the hand), and continuous vibrotactile stimulation (mechanical vibrators). In a sequential rest–activation paradigm with two bolus injections of FDG, Ginsberg et al.[29] found that tile sorting was accompanied by increased metabolism only in the somatosensory cortex contralateral to the stimulated hand. Having subjects squeeze an examiner's finger in response to tracing a one-digit number on the palm of the hand did not lead to a detectable increase in any specific area of the brain relative to resting conditions. Continuous vibrotactile stimulation also produced nonsignificant changes in activation levels.

Ginsberg et al.[30] showed that similar tactile discrimination tasks resulted in significant increases in glucose utilization in both the ipsilateral and contralateral hemispheres. The results suggested that an attentional factor contributed strongly to the changes in activation. They also suggested that at least some subjects may have been "primed" by their pre-scan exposure to the tile-sorting tasks. All subjects receiving right-hand stimulation showed greater metabolic activity in the contralateral area than did subjects who performed the task with their left hand. The greater metabolic activity in response to right-hand stimulation may indicate greater left-hemisphere involvement in cognitive tasks that have tactile and object-recognition components.

Taken together, studies assessing the functional organization of the cortex measured by changes in brain activity levels in response to somatosensory processes indicate that tactile-recognition tasks do not provide evidence of specific sites responsible for haptic discrimination. Initial studies showed that stimulation resulted in focal increases in brain areas contralateral to the side of tactile stimulation. However, more recent studies suggest that the left hemisphere contributes relatively more to the cognitive component of object-recognition tasks and that global increases in brain activity from resting to activation levels are noted throughout most areas. These nonspecific shifts may reflect changes in activity due to attention and arousal as a consequence of the task. They may also reflect changes resulting from "priming" that may have occurred when the subjects were previously exposed to the sorting tasks.

NEUROPSYCHOLOGICAL PROCESSES DURING RESTING STATES

In studies of resting states and cognitive activity, subjects are typically scanned while in a supine position with their eyes covered and their ears plugged.[31,32] Cognitive-test scores obtained either before or after the scans are then correlated with resting-state metabolic values in a group of subjects. This model has obvious advantages when dealing with cognitively impaired subjects or with limitations imposed by the scanning equipment. However, there are significant problems associated with interpreting data obtained from this paradigm. Resting metabolic values may not reflect the actual status of the cortex in response to cognitive tests. While engaging in tasks with neuropsychological components, subjects are frequently at an optimal level of attention and functioning. But in studies that do not use an activation task, patients' levels of cognitive activity may be extremely variable during rest. The magnitude of difference in FDG uptake between subjects caused by this uncontrolled variation could be larger than differences in FDG uptake resulting from cognitive functioning.[16]

In addition, intervening events may lead to significant changes in metabolic status. Duara et al.[33] have demonstrated significant changes in repeated scans of resting normal subjects taken two weeks apart. These unsystematic differences are attributed to patients' cognitive activity during the resting scan; changes in cortical activity over time may be misinterpreted as sources of "error" or as treatment variance not readily explainable within the research design. Despite these limitations, resting-state scans may be the only way to obtain data from cognitively impaired patients or when the test materials produce unwanted activation during the scan.

Ferris et al.[34] correlated the relative rates of FDG uptake in the brain at the level of the basal ganglia to objective measures of cognition in seven patients with the presumptive diagnosis of Alzheimer-type dementia. Cognitive measures included immediate and delayed recall of a paragraph, paired-associates learning, a design-recall measure, and two rating scales of mental status. They found large and statistically significant correlations (range, r_{xy}=.73 to r_{xy}=.92) between glucose metabolism in the gray and white matter of the frontal cortex and mental status variables. They found somewhat fewer but comparable correlations between metabolism and such variables in the caudate, thalamus, and temporal lobes (range, r_{xy}=.70 to r_{xy}=.89). No significant correlation between the ranking of cortical atrophy based on CT scans and regional FDG uptake was found, but a significant association between ratings of the amount of ventricular dilation and the rate of glucose utilization in the caudate was found. Because FDG uptake in the caudate also showed strong correlations with the mental-status variables (range, r_{xy}=.83 to r_{xy}=.85), the relationships between structural, metabolic, and cognitive functioning require more study.

Ober et al.[35] compared clinical ratings of various components of drawing tasks to FDG in a sample of demented patients. They reported that FDG uptake correlated in the temporal-parietal and occipital regions of the cortex with drawing recognizability, accuracy of configuration, attention to detail, and accuracy of detail, but it did not correlate with activity in the frontal or presylvian regions. The results suggest that metabolic activity in bilateral-posterior cortices is related to the visuoconstructive deficits shown in patients with senile dementia.

Farkas et al.[36] found that the degree of cognitive impairment in patients with dementia was significantly correlated with the rate of FDG uptake in the frontal cortex, the temporal cortex, and the caudate nucleus at a level horizontal to the basal ganglia. Friedland et al.[37] correlated more detailed neuropsychological test results to cortical metabolism in Alzheimer patients. They found that the Mattis Dementia Rating Scale[38] and the verbal subtest of the Wechsler Adult Intelligence Scale (WAIS-VIQ)[39] scores correlated with a ratio of right-frontal to left-frontal glucose utilization. However, the performance subtest (WAIS-PIQ) correlated negatively with the ratio of right frontal to left-right temporo-parietal glucose activity. In another study, levels of glucose metabolism during resting states were found to be significantly correlated with the WAIS-FSIQ, the Wechsler Memory Quotient,[40] and the Mattis Dementia Rating Scale scores in a mixed group of demented and normal control subjects.[41]

Chase et al.[42] examined the relationship between cerebral FDG uptake and performance on tests measuring language, praxic skills, and memory in Alzheimer subjects who had prominent language, visuoconstructive, or memory losses. Metabolism in both hemispheres was correlated with overall intellectual functioning. The WAIS-PIQ scores correlated with glucose metabolism in the left but not the right hemisphere, and WAIS-VIQ scores correlated with left hemisphere and whole brain metabolism. Glucose metabolism for two aphasic patients was 18% lower in the left temporo-parietal region of the cortex than in the same region in the opposite hemisphere. In four patients with primarily visuoconstructive deficits, the glucose metabolic rate was 32% lower in the right temporal-parietal area than in the left temporo-parietal area. In contrast, amnestic patients showed small right-left differences in this area. When patients with Alzheimer's disease were compared to normal controls, glucose metabolism throughout the brain was lower for patients with Alzheimer's disease, but the reductions were much larger in the cerebral cortex compared with subcortical structures, and in the posterior portion of the brain compared with the anterior portion.[43,44]

Chase et al.[45] studied whole-brain metabolism in patients with Alzheimer's disease who had significantly lower scores on the Mattis Dementia Rating Scale, WAIS, and Wechsler Memory Scale than control subjects. Similar to previous studies, whole-brain metabolism was found to be lower for the patients with Alzheimer's disease, with greater metabolic reductions in the posterior portion of the brain than in the anterior. The largest differences were found in temporal cortex. Glucose metabolism also correlated with symptom duration, all measures of intellectual functioning, memory scores, and ratings of dementia.

Chase et al.[46] analyzed the relationship between resting cortical FDG uptake to WAIS subtest scores in cognitively impaired subjects. There were significant correlations among the WAIS variables and glucose metabolism (range, r_{xy}=.70 to r_{xy}=.76). The scores on the verbal subtest were more closely related to cortical metabolism in the left hemisphere (r_{xy}=.68) and, in particular, to metabolism in the left temporal lobe (r_{xy}=.76); the nonverbal scores were correlated with metabolism in the right hemisphere, especially in the right parietal lobe (r_{xy}=.70). In addition, Grady et al.[47] have shown that impaired dichotic speech performance in patients with dementia of the Alzheimer type is related to reduced glucose metabolism in the temporal lobes.

In contrast to studies using impaired subjects, studies of resting cerebral metabolism in normal subjects have not shown significant correlations with performance on neuropsychological tests. Duara et al.[48] and Haxby et al.[49] did not find a significant association between rates of

FDG uptake and scores on the WAIS or the Benton Visual Retention Test[50] in normal healthy subjects. In another study,[51] lateralized rates of FDG uptake did not correlate with either language functioning (measured with a sentence comprehension test) or visual spatial processing (measured with a copying task). The authors speculated that the lack of significant correlations may have resulted from the restriction of the range of the scores, but it could also have resulted from the use of difference scores.[52]

NEUROPSYCHOLOGICAL FUNCTIONS DURING ACTIVATION

Gur et al.[53] carried out the first study of differences in FDG uptake in which subjects were scanned twice during two different types of stimulation—verbal and spatial tasks. The verbal task consisted of solving verbal analogies,[54] and the spatial task involved comparing the lengths of tachistoscopically presented lines.[55] The investigators found that four regions of the brain showed significant, lateralized effects in response to these activation tasks: the superior temporal, the inferior parietal, the inferior frontal, and the frontal eye field. Higher metabolic activity was observed in these areas in the left hemisphere during the verbal activation task and in the right hemisphere during the spatial task. Of considerable interest was the observation that the differences were larger in the right hemisphere during the spatial task. Furthermore, the spatial task was associated with more generalized variations within the right hemisphere. The larger differences seen in the right hemisphere could have resulted from the putative role of this hemisphere in tasks that involve attention, as the authors speculated. However, Phelps[19] interpreted his PET scan data, in which bilateral frontal lobe activation was obtained during an auditory memory task, as indicating significant bilateral frontal involvement in attentional processes. To resolve these conflicting results, future studies will need to examine the differential effects of cognitive tasks beyond those changes seen when the subject switches from the resting state to tasks requiring attention. Data from such comparisons should be analyzed by statistical procedures that account for covariance, rather than by simple difference scores.[52,56]

Bartlett et al.[57] used partial correlations to control for individual differences in overall brain metabolism and compared brain metabolic rates in stimulated and unstimulated conditions. They found no significant within-hemisphere correlations during the unstimulated condition, but significant correlations were observed during a language-stimulation task, particularly in the left regions of the brain. In addition, the pattern of correlations that emerged suggested that the left inferior frontal area may enlist other areas within the left hemisphere for the task. Finally, they noted that activity in the right inferior frontal region was unrelated to activity in other areas of the brain. Their methodology successfully highlighted the shift toward more organized levels of activity in areas of the brain traditionally thought to be important in language processing. Moreover, because controls for individual differences in metabolic activity were employed, the results suggest that the left inferior frontal region may play a role in organizing brain activity in response to tasks demanding sustained attention.

In a study of memory processes in normal controls and patients with dementia, Miller et al.[58] compared resting-state scans to scans obtained while subjects performed a verbal recognition task. As expected, control subjects performed the task better than did subjects with dementia. Control subjects also showed larger increases in FDG uptake in the left hemisphere than in the right hemisphere. Responses to the recognition task by patients with dementia occurred at the chance level, suggesting that either there was a lack of memory processing or they were not able to comprehend the task. However, the pattern of brain activation in patients with dementia was similar to the pattern seen in control subjects, although activation was reduced. The pattern of higher activation levels in the right hemisphere of nonactivated control subjects and decreases of this disposition toward the right during memory activation bears further investigation.

Parks et al.[59] compared resting FDG metabolic rates with rates obtained following verbal fluency activation in normal subjects and found a 23.3% increase in the absolute metabolic rate throughout the cortex during the oral production of words. When regional FDG uptake levels were normalized to the occipital lobe, the greatest degrees of cortical activation were found in the temporal (27%) and frontal (25%) lobes of both hemispheres. The parietal and occipital lobes showed only 18% to 19% increases in glucose metabolism over resting-state values, and these results were consistent with previous research showing frontal-lobe involvement in verbal fluency.[60] The bilateral temporal activation may have resulted from the role of the temporal region in oral production, from the effects of attention on level of cortical arousal, or even from auditory stimulation, as subjects could hear themselves talk. An unexpected result was that verbal fluency performance was negatively correlated with FDG uptake. That is, individuals with lower fluency scores tended to have greater rates of glucose metabolism.

In a different study, Ginsberg et al.[29] noted that subjects with low left-right metabolic asymmetry were able to sort

coins quite easily, and the subject with the least asymmetry was able to perform the task almost effortlessly. Haier et al.[61] also found negative correlations between FDG uptake and cortical activation induced by abstract problem solving in healthy male subjects. Metabolic rates increased in the posterior portion of the cortex during performance of the Raven's Advanced Progressive Matrices[62] exercise compared with rates obtained during a visual-vigilance task.[63] However, performance on the complex Raven's task and bilateral FDG uptake in several brain regions (the anterior portion of the frontal lobes and the superior middle and inferior portion of the parietal lobes) showed significant negative correlations: subjects who performed well had lower FDG uptake rates. The apparent paradox of an inverse relationship between metabolism and level of functioning might result from between-subject differences in the efficiency of their cognitive strategies. Subjects who perform poorly may have inefficient strategies that require a higher level of energy consumption. Whether glucose metabolism is a measure of effort or performance remains to be determined.

A recent modification to PET scan procedures has allowed researchers to study glucose metabolism in response to two different cognitive states within a single extended PET procedure. The procedure involves a double injection of FDG and was developed by Chang et al.[64] Immediately following the completion of the first PET scan, a second injection of FDG is administered. This technique was made possible by the development of a mathematical model that predicts the concentration of the radiopharmaceutical agent remaining in the brain from the first scan, allowing readings made during the second scan to be adjusted. As a consequence, the subject serves as his own control.

Using this double injection procedure, Duara et al.[65] explored the specificity of involvement of the left frontal lobe in verbal fluency tasks. Radioactivity levels obtained from a scan taken while the subject counted out loud were subtracted from levels obtained from a scan made during a verbal fluency task; the result reflected differences in activation patterns between the two tasks. Preliminary findings indicated that the areas of greatest change were in the orbito-frontal region of the left hemisphere. This use of an attention-requiring task clearly enhances the researcher's ability to elucidate neuronal networks associated specifically with different types of neuropsychological processes. The scan-subtraction technique also provides partial control for error variance.

The utility of PET techniques for studying cognition has also improved through the use of isotopes with short half-lives. Serial doses of specific ligands permit multiple brain images to be obtained from cognitive sets with different hierarchical arrangements. For example, Roland[66] has suggested that the working human brain processes visuospatial information through multiple cortical neuronal networks. This hypothesis was tested by Roland et al.[67] using a within-subject, repeated-measures design. A "pretrained" visuospatial task was designed, in which the subject took an imaginary walk out his front door and made alternate left and right turns at successive street corners. Emphasis was placed on attention to visual details, which were assessed in a post-task debriefing. All subjects reported experiencing virtually constant visual images. Pretraining allowed the task to be performed without further instructions from the investigators or verbal responses by the subject, who was lying motionless with closed eyes in a quiet room. Two scans were taken of each subject. The rate of [^{15}O]-O_2 extraction in the brain (half-life=123 secs) following inhalation of the gas was measured. The first scan was obtained during the resting state; the second was obtained during performance of the pretrained visuospatial task. Comparison of the scans revealed that visuospatial processing was associated with a general increase in oxygen metabolism in most cortical areas. The largest increases occurred bilaterally in the parietal and frontal lobes. This metabolic increase in oxygen consumption was coupled to increased regional blood flow. The authors believe that their results support their hypothesis that multiple cortical fields are activated during visuospatial cognition.

Clever implementation of the multiple-imaging technique is illustrated in recent experiments by Petersen et al.[68] They designed a within-subject, repeated-measures study of single-word processing based on a hierarchical subtraction model. Scans of ^{15}O-labeled water were obtained during four hierarchically arranged situations. The subject first visually fixated without any word presentation; single words were then passively viewed; the same words were then simultaneously viewed and articulated; and finally the words were both viewed and their usage described. Difference scores obtained by serial subtraction of these hierarchically arranged scans suggested that visual information from occipital cortex has access to output coding (articulatory coding, motor programming) without undergoing phonological recoding in the temporal cortex. Simple pronunciation of the words presented did not activate the frontal lobes, while semantic processing activated frontal rather than temporal regions. These results were further interpreted as supporting the parallel-multiple route models of cognitive processing.[69]

In a series of articles extending scan subtraction methodology, Posner et al.[70–73] developed a crucial conceptual framework previously missing in the PET literature on cognition. They proposed a coherent hypothesis of the neurophysiological basis of attention and the elementary operations of language and semantic associations. Ac-

cording to their hypothesis, attention is maintained as a distinct function carried out by a distributed network in many anatomical areas. Thus, attention is neither a property of a single center nor a function of the whole brain. These authors[72] distinguished their model of attention in the following statement:

> This form of localization of function differs from the idea that cognitive tasks are performed by a particular brain area. Visual imagery, word reading and even shifting visual attention from one location to another are not performed by any single brain area. Each of them involves a large number of component computations that must be orchestrated to perform the cognitive task (p. 1630).

They further stated that "this idea fits generally with many network theories in neuroscience and cognition" (p. 1627).[72] Finally, in reference to PET research in attention, Posner et al.[72] state that "a systems level analysis provides a framework for the more detailed studies that must follow" (p. 15).

SYSTEMS EFFICIENCY

We have outlined the tenets of "systems theory" applications to PET and neuropsychological test performance elsewhere.[74] Briefly, the majority of PET findings have neglected to examine the proportional contribution of multiple brain areas that work together during performance of many tests of higher cortical functioning. Systems theory is in counterpoint to the focal localization hypothesis, which suggests that a complex neuropsychological test can involve primarily a single cortical area. For example, performance on certain neuropsychological tests, such as verbal fluency[75] or the Wisconsin Card Sorting Test,[76] has been attributed to frontal lobe functioning. When performed in conjunction with PET activation paradigms, both word fluency and card sorting demonstrate multiple areas of cerebral activity compared to baseline metabolism.[77,78]

The concept of efficiency should be included in the explanation of activation of multiple areas. Efficiency is the ability to produce a desired effect with a minimum of effort, expense, or waste.[79] Efficiency exemplifies the optimal functioning of the normal human brain and how it may play an important part in understanding neuronal networks and cognition. PET research on neuropsychological mechanisms can now support such an observation.

We hypothesize that there are four significant components of brain efficiency: neurochemistry, the structural integrity of the cortex, a topographical distribution of networks, and a strategy of cognitive operations. For each of these systematic divisions, we contrast normal human brain functioning with brain function in patients with Alzheimer's disease, which has been well researched with PET techniques.

Brain neurochemistry. The neurochemical component of our concept of brain efficiency includes the relative contributions of neurotransmitter activity from release to postsynaptic neuronal activation and is essential to normal cognitive processes. Neurochemical deficiencies in Alzheimer's disease have been correlated with neuropsychological deficits, including memory loss,[80–83] and the levels of acetylcholine, norepinephrine, serotonin, and other neurotransmitters are all markedly reduced in the cortex of patients with Alzheimer's disease.[84–87] However, the total number of neurons associated with all of these transmitters is less than 1×10^{-5} of all the neurons in the cerebral cortex.[88] PET ligand research with glutamate-receptor antagonists[89] and other tracers should open avenues to study neurochemical pathways in patients with Alzheimer's disease and normal controls.[90,91]

Cortical structural integrity. The structural integrity of the cortex sets the stage for cortical and mental activity. In normal aging, neuropsychological functions can be intact, despite the presence of neuropathological changes.[92,93] However, the structural changes seen in patients with Alzheimer's disease are usually far more pronounced. In Alzheimer's disease, numbers of plaques and neurofibrillary tangles increase, and severe synaptic loss is seen in the hippocampal complexes and in certain regions of the neocortex. The diverse pathology of Alzheimer's disease may act in concert with the more global neuronal losses associated with normal aging, resulting in the clinical picture of dementia.[94] Accordingly, CT and PET studies show that structural brain changes are more salient during normal aging than the biochemical changes while the additional disruptions in Alzheimer's disease are associated more with the biochemical changes.[95] Moreover, neuropsychological tests of complex short-term memory, spatial abilities, and language functions are better predictors of cognitive deterioration in patients with Alzheimer's disease than are CT measures.[96] In addition, changes in cortical metabolism in patients with Alzheimer's disease usually precede neuropsychological deficits.[97]

Topographical distribution of neuronal networks. Perhaps the most significant contribution to cognition research utilizing PET has been the use of ^{15}O-labeled water to obtain multiple scans of a single subject in one sitting, a technique developed by Peterson et al.[68] With this technique, these researchers have provided evidence of the topo-

graphical distribution of neuronal networks involved in attention activities and semantic associations. Marshall[98] has observed that their "results appear to offer direct confirmation of a reading route that does not involve obligatory phonological recoding of the visual stimulus before semantic access" (p. 561).

Results from these studies support a theory of *parallel-distributed processing* (PDP) in neuronal networks.[60] Objections to PDP theory arise from observations that human cognitive functions, especially language, usually follow logical, sequential, and grammatical rules, and PDP methodology does not provide a clear basis for syntactic structure.[99] In spite of these schematic differences, Fodor and Pylyshyn[99] state that a few PDP models "could still be held that networks sustain *some* cognitive process" (p. 68).

PDP research draws on early attempts to model cell assemblies with computers[100] and on later models of visual pattern analysis[101,102] and semantic networks[103] involving intricate mathematics. Considerable evidence supporting PDP theory has also arisen from the animal literature. This evidence suggests that multiple areas of the brain function in concert to effect cognition.[104–107] Furthermore, columnar histological aggregates which have been identified in animals and humans directly support the simultaneous processing of neural information in networks.[88,108,109] These organizational concepts may be applied to human models of associative learning[110] and networks,[111,112] and add to evidence of the existence of both serial and parallel neuropsychological systems.[113]

Problems may arise when PET data are applied to the integration of "serial" and "parallel" models because of limitations in isotope selection and PET scanning methodology, especially temporal resolution. For example, how do we interpret a resting-state FDG scan and a cognitive-activation FDG scan initiated on different days? Can resting-state and cognitive-activation data from a single FDG double-injection scan[64] be compared? Is analysis of data obtained by subtracting an FDG resting-state scan from a single FDG cognitive-activation scan sufficient to allow interpretation of models of cognition, or must multiple ^{15}O-labeled water scans be performed?

An essential question involves the degree of metabolic activity that should be attributed to the performance of a particular neuropsychological task. Many studies have shown a positive correlation between increased metabolism and the involvement of specific brain regions in the performance of discrete sensory operations, but the relationship between levels of metabolic response and complexity of neuropsychological function is less clear. For example, negative correlations have been found between metabolism and neuropsychological test performance for Ravens Advanced Progressive Matrices[61] and verbal-fluency tests.[59] Haier et al.[61] speculate that the negative correlation is due to inefficient neural circuits contributing to poor performance, and efficient circuits using less energy but providing optimal performance. Inefficient neural operation could arise from many different functional levels. For example, dysfunctional neurochemical systems or developmental inadequacies in particular neural structures could result in poor feedback. Inadequate recruitment and poor organization of processing elements might lead to inefficient communication within topographical assemblies of neuronal networks. Ineffective implementation in particular serial and parallel systems could lead to an inability to solve the neuropsychological task. Moreover, although an excess of neuronal networks may be necessary to maintain cerebral function in the face of age-related cell loss in the brain,[48] utilization of redundant circuits could lead to inefficiency. Longitudinal studies of neuropsychological and cerebral metabolic changes in Alzheimer's disease suggest that these patients lose their reserve capacity in a progressive manner, presumably because alternative circuits are lost. Grady et al.[114] have suggested that "the ability of the neocortex to compensate for metabolic dysfunction may explain the plateaus seen in some patients in which little change is seen in cognitive performance, with the appearance of new impairments signalling the breakdown of the compensatory mechanisms" (p. 590).

Strategies of cognition. The role of strategy in cognitive operations is illustrated in the studies by Mazziotta et al.[21] on audition. They found that subjects with substantial musical training were able to analyze auditory stimuli in a manner that allowed metabolism to supersede traditional auditory pathways. Assuming comparability of subjects and excepting the history of prior musical training, the differences they observed in lateralized metabolism are difficult to explain in terms of individual differences in neurochemical or cortical structures. Subject selection was based on subjects' levels of musical sophistication. Perhaps musical training develops analytic strategies for acquiring this particular skill or builds on a genetic predisposition facilitating the skill's development, leading to an improved ability to organize auditory stimuli efficiently. These findings,[21] combined with Hunt's[115] observations on information-processing strategies, have led us to suggest that cognitive strategy is a pervasive organizing mechanism in which a person processes internal and external stimuli.

It is not clear how a particular cognitive strategy is reflected by lateralized radiopharmaceutical distribution during complex neuropsychological tests. Before generating a cognitive activation paradigm based on PET techniques, extensive neuropsychological evaluation would

be needed to generate dispositional hypotheses concerning the subject's cognitive strategy. Alternatively, the effects of strategy could be partialled out by a postscanning statistical analysis (e.g., analysis of covariance). For example, when assessing field-independent or field-dependent processes[116] in perception research, neuropsychological tests such as the Rod and Frame Test[117] or the Embedded Figures Test[118] might provide the most useful data.

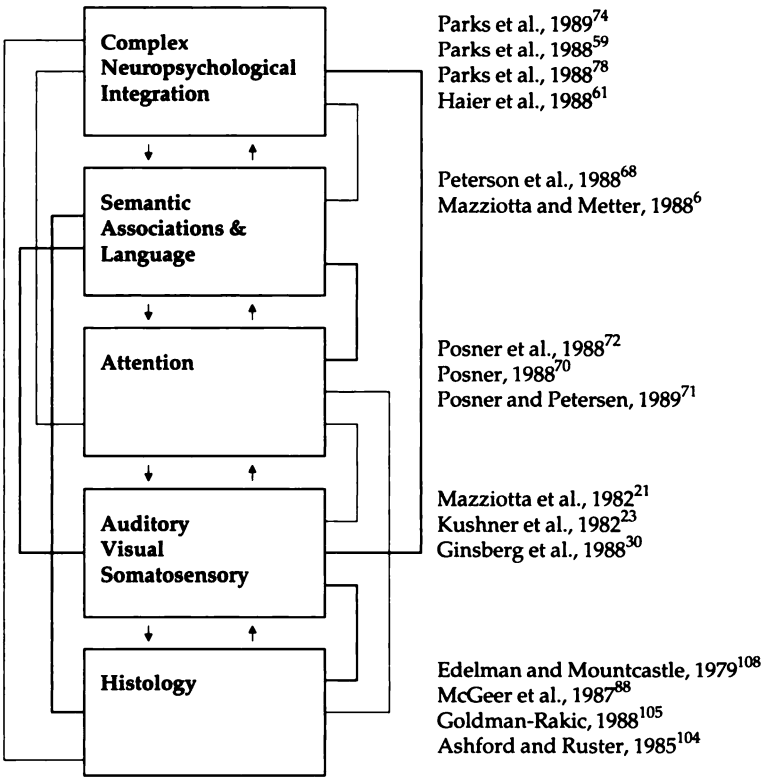
PET research with neuropsychological assessment has typically involved administering standardized tests, such as the Halstead-Reitan battery.[119] Another approach, the Boston Process,[120] utilizes many different neuropsychological tests.[121-124] While both neuropsychological assessment procedures yield a quantitative scoring system, the hallmark of the Boston Process is the resulting "careful systematic observations of the problem-solving strategies used by patients (i.e., the way they successfully solved or failed to solve each problem presented to them" (p. 67).[125] For example, performance on the Block Design subtest of the Wechsler Adult Intelligence Scale-Revised[126] can provide information on the

> featural priority (emphasis on details), contextual priority (emphasis on the gestalt), and hemispatial priority (the tendency to work on one side of visual space). . . . Right hemisphere-damaged patients tend to work on the right side of visual space and to use a detail-oriented strategy, whereas left hemisphere-damaged patients tend to work in the reverse field and with the reverse strategy (p. 64).[127]

Using the Boston Process[128,129] enables researchers to clarify factors on multifactorial standardized tests and leads to a better understanding of the roles of individual variables, task variables, and stimulus parameters in brain–behavior relationships. The assessment procedures of the Boston Process can be adapted to different types of content (e.g., verbal and nonverbal), and all modalities of input and output (e.g., auditory, visual, sensory, and motor).

The recent quantification of the qualitative aspects of strategy will improve methodology for PET cognitive-challenge studies and will lead to more precise neuropsychological test batteries. Further examination of this strategy-analysis approach to PET studies is needed to decrease experimental variance, particularly in studies of subjects who have unique skills and who therefore may use idiosyncratic strategies. It remains to be seen to what degree, in subjects whose performance on neuropsychological tests is comparable, different cognitive strategies will cause different regional radioisotope distributions. For example, would dissimilar problem-solving strategies employed during the Block Design subtest differentially affect PET activation measures?

FIGURE 1. Systems efficiency model



The systems efficiency model provides a possible interaction pattern that would account for differences in cognitive strategies. Figure 1 represents a schematic illustration of the systems efficiency model. The paradigm allows for the existence of both serial (vertical arrows between boxes) and parallel (circumscribed lines to the left of the boxes) neuronal networks. This representation suggests a hierarchical model able to go from complex to simple and from simple to complex cognitive functions, while the distributed networks accept differentially selective inputs or outputs that can be initiated at any level in the matrix. The nature of the cognitive task may contribute to the routing of neuronal information.

FUTURE DIRECTIONS

Most PET studies employing an activation paradigm have examined sensory-cortical pathways in human subjects. The results have generally supported such traditional concepts as cross-lateral representation with lateralization of verbal tasks in the dominant hemisphere

and nonverbal processing in the nondominant hemisphere. Because the studies have concentrated on the organization of the primary sensory areas, they have yet to tap the vast potential of PET technology to elucidate the brain processes that produce goal-related behavior. PET studies to date have inadvertently reinforced the notion that progress will be achieved by searching for a one-to-one correspondence between regional neuroanatomy and brain function. More detailed studies of the cognitive significance of global shifts in geographically and histologically diverse areas of the brain are needed to understand the relationship of structure to process.

Approaches that focus on the relationship of activity in multiple areas of the brain to cognitive tasks are a step in the right direction. Such studies allow us to examine the shifting patterns of arousal in relation to tasks designed to elicit specific cognitive responses. Additional tasks designed to produce or to avoid the desired activity based on the double-disassociation model[113,130,131] should speed our understanding of brain organization. The use of related path-analysis techniques[132,133] will allow changes in diverse areas over time to be analyzed. Methods like these, which address the relationship of multiple neuronal networks, allow patterns of correlations between areas of brain to be compared in both normal and pathological conditions. However, statistical tests based on comparison of variance-covariance matrices are very sensitive to rejection of the null hypothesis,[134] and Type I errors could occur at a far greater rate than the alpha level chosen by the experimenter. Researchers must therefore be aware that experiments might yield statistically significant but clinically insignificant results. Moreover, reliability or internal consistency cannot substitute for validity.[135]

A related problem facing researchers developing PET techniques is the need for a uniform method for extracting data from scans. Scoring procedures that standardize activity from different regions of interest may produce general correlations among brain metabolic parameters but obscure a precise understanding of how multiple areas of the cortex are organized into neural networks that reflect cognitive processes. While analyses using correlational methods may partially offset problems associated with standardization of scores and although they can sometimes produce positive results in the face of violations of underlying assumptions, they cannot substitute for a rational plan for collection of data.

Many studies have included patients with diffuse and severe neuropathology. These patients are often so impaired that they cannot attend or respond differentially to the assessment procedures. They may function at near chance levels, and it is extremely difficult to interpret the results in such circumstances because it is impossible to know exactly what determined the subjects' responses. Including severely impaired subjects who have multiple-system diseases also creates problems for determining what particular dysfunction or dysfunctions produced an abnormal pattern of brain arousal. Interpretations of PET-scan data from studies of compromised brain function may reach an asymptote with respect to what they can contribute to our understanding of normal regional neuropsychological brain functioning.[136,137]

Studies to generate new hypotheses about the proportional contribution of many neural networks in the brain to cognitive task responses are needed. These studies will no doubt involve activation procedures, which offer the only means of determining which features of the tasks performed are critical to producing changes in metabolism. In addition, these techniques allow researchers to control for preexisting differences between subjects and permit standardization of the subjects' mental state by controlling their behavior during intra-scan intervals.

Activation studies will likely involve cortical arousal in response to sustained attention, motor dexterity, visual discrimination, and memory tasks. A likely source for new PET paradigms will come from the investigation of well-established neuropsychological phenomena such as cued recall,[138] crossed aphasia,[139] olfactory recognition, and mirror motor activity. Experimental paradigms will be improved by accounting for factors such as sex differences, handedness, and elements that interfere with performance, including anxiety, fatigue, and habituation to task demands.[78]

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