Thinking Nuclear Medicine–PET Activation

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PET activation, although restricted to a limited number of research centers, is currently the gold standard for mapping functional areas of the brain. This paper outlines how and why activation studies are performed and reviews the major uses of this technique. Special emphasis is on cognitive neuropsychology including the results of a project designed to map the areas of the brain responsible for controlling automatic counting and simple calculation. These fascinating studies are, by definition, a part of nuclear medicine. As such, we argue that knowledge of PET activation is an essential component of professional development and that, given opportunity, commitment and the will to learn, nuclear medicine technologists have the potential for involvement, collaboration or leadership in this area of research.

Key Words: PET activation; cognition; neuropsychology; automatic counting; intrasubject averaging; coregistration

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PET plays an integral role in diagnosing an eclectic range of neurological disorders. PET's major advantage over other diagnostic modalities lies in its ability to demonstrate brain function, such as blood flow, metabolism, receptor analysis and protein synthesis (*1*). These functional capabilities provide sensitive methods for diagnosing cerebrovascular disease and dementias including Alzheimer's disease. PET also contributes significantly to the investigation of epilepsy, the grading and treatment monitoring of brain tumors and several psychiatric disorders such as schizophrenia, obsessive-compulsive disorder and manic depression.

PET activation studies measure the changes that occur in cerebral blood flow (CBF) during different mental processes and thus are able to map areas of functional neuroanatomy. At the present time, activation studies using PET are restricted mostly to large research hospitals. Despite a lack of direct clinical application, PET activation is gaining increasing prominence as a research method in areas such as psychiatry, neuropsychology and neurology. Research in these areas is increasing our knowledge of normal brain function and structure and has the potential to assist in diagnosing and monitoring therapy for a range of neurological disorders.

Research activity is integral to the development of any profession (*2,3*), including nuclear medicine technology. PET activation's unique ability to effectively demonstrate the way we think attracts experienced researchers from other fields with little knowledge of PET, nuclear medicine or radiation. This situation presents nuclear medicine technologists (NMTs) with opportunities for involvement, collaboration or leadership in research, depending on their level of commitment and their ability to learn. Experienced NMTs already possess a large portion of the knowledge and skills necessary for work with PET activation. Their expertise in intravenous injection, patient comfort, patient positioning and radiation safety as well as their experience on clinical trials with new drugs and in obtaining informed consent provide them with skills that are directly applicable and transferable to PET activation. Likewise, the ability to adapt to new and changing technologies, to develop and improve scanning protocols including acquisition and analysis techniques, and experience interacting with a range of health professionals (*4*) are common to the role of both the NMT and the practitioner who works with PET activation.

The potential for NMTs to become collaborators in PET activation research could be enhanced by further developing their knowledge and expertise in PET technology, co-registering data, and submitting research grant and ethics applications. In addition to the above, NMTs wishing to initiate research of this type also would need to acquire knowledge of concepts related to cognition, functional neuroanatomy and methods of psychological research.

In this paper we argue that PET activation, although currently limited to research centers, has the potential for wider clinical application in the future. We believe that knowledge about this growing area of nuclear medicine should be part of the professional development of all technologists. Involvement in PET activation research affords an opportunity for technologists to use their specialized expertise in nuclear medicine (*4*)

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to ensure best practice in a truly multidisciplinary environment. We outline how and why activation studies are undertaken, examine their limitations and describe the major disciplines that make use of PET activation. Finally, a PET study involving automatic counting and arithmetic calculation in cognitive neuropsychology is presented to illustrate this fascinating and important area of nuclear medicine.

WHAT IS BRAIN ACTIVATION?

Brain activation operates on the principle that physiological changes in the brain, such as changes in blood flow and electrical activity, underlie all mental events. In brain activation research these physiological changes, known as activations, are used to locate the areas of the brain involved in specific mental processes (*5*). Experiments typically involve measurement during two complementary mental processes, such as reading words and repeating words (*6*). The data from these mental events are compared by subtracting activation during one mental process from activation during the other to obtain information about the areas of the brain involved in both tasks.

The relationship between CBF and brain activity is central to the rationale of activation studies (*7*). Thinking, or cognitive activity, increases metabolism in the brain including oxygen consumption. As oxygen is carried in the blood, an increase in oxygen requirement leads to a corresponding increase in blood flow. Therefore, increases in CBF reflect mental activation occurring in the brain. The higher the increase in CBF, the higher the contribution of the area to the mental activity. During any thought process or mental activity, subtle changes in CBF occur in multiple areas of the brain. Therefore, it is essential to differentiate between CBF resulting from the mental activity being studied and CBF resulting from background mental activity, such as auditory, visual or discomfort stimuli.

Several methodologies, such as electroencephalography (EEG), event-related potential mapping (ERP) and magnetoencephalography (MEG) (*5,8*), have gained widespread use and have the advantage over nuclear medicine of not using radioactivity. However, the image resolution of these is relatively poor compared to PET. More recently, functional MRI (fMRI) (*9–11*), with its excellent spatial resolution of 1–4 mm, has gained increasing prominence in mapping brain function. However, while less invasive than PET, its use of magnetism and the levels of noise produced by the process do not, at the present time, allow its easy use in cognitive activation.

The ready availability of ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) and SPECT presents the potential for SPECT activation studies to be performed extensively. HMPAO's brain uptake time of 4 min is a workable period in which to measure CBF changes during mental activity. On the down side, ^{99m}Tc's 6-hr physical half-life presents considerable blood background difficulties in performing more than one mental activity study on the same day, making 2-day protocols the norm for SPECT activation. SPECT activations require the relatively large changes in CBF usually associated with lower order brain events. For example, activation studies using simple stimuli, such as light and sound, have shown changes in cerebral perfusion of 17%–19% (*12–14*), thus successfully mapping gross auditory and visual areas of the brain. This is in contrast to PET studies where higher order mental events such as attention, language and memory (*14*) have been mapped after relatively small CBF changes of only 2%–10% (*15,16*). Thus, while SPECT has a role in single-activation protocols for epilepsy or in response to drug therapy in schizophrenic patients, it is far from ideal in performing higher order cognitive brain mapping studies.

PET ACTIVATION STUDIES

PET activation studies typically require subjects, usually normal volunteers, to lie in the PET scanner for 1–2 hr. This allows time for transmission scanning, attenuation correction and verifying positioning, followed by a series of seven to 13 activation runs at a minimum of 8-min intervals between runs. Each activation run requires an intravenous injection of water labeled to ^{15}O ($H_2{}^{15}O$). The 2-min half-life of $H_2{}^{15}O$ means that after only 8 min, or four half-lives, $H_2{}^{15}O$ activity returns to background levels.

At the start of each activation run, the PET acquisition and $H_2{}^{15}O$ infusion (through a small vein in the subject's arm) is begun (mean injection time 60 sec; mean activity per injection 20 mCi) to produce an increasing brain counting rate for approximately 100 sec. A background frame is acquired for the first 30–50 sec, depending on the perfusion rate of each subject, to ensure peak cerebral activity of $H_2{}^{15}O$ before the cognitive task begins. At peak cerebral activity the cognitive task begins for a 100-sec period (the foreground frame). On completion of the cognitive task, subjects are able to relax until the next activation. The repeated activation runs serve to increase the statistical validity of PET to map areas in the brain responsible for each activation task.

Adequate head restraint is necessary for all studies (*17*) because even the simplest PET activation study lasts 1–2 hr and some head movement is inevitable. Individually molded head-restraint systems produce excellent results, although they are not 100% effective even with cooperative subjects.

Three-Dimensional Mode

Until recently all PET activation studies were performed using two-dimensional mode scanning. This required the use of collimation in the PET scanner to reduce backscattered radiation and meant that PET detectors had limited sensitivity due to the collimators. According to radiation safety guidelines used in Australia, the total dose from a PET study cannot exceed 120 mCi. Two-dimensional PET studies, with lower sensitivity, require higher activity per activation than three-dimensional studies, limiting them to only seven activations per study. In contrast, the use of three-dimensional acquisition (*18*) with its increased sensitivity has provided the opportunity to scan up to 13 activations per subject without exceeding safe radiation dose levels (*19*). The three-dimensional mode's ability to almost double the number of activations per subject provides a significant increase in the statistical power of PET activation research projects that typically have only 4–16 subjects.

Coregistration

The ability to precisely locate functional brain areas repeatedly on sequential images is a concern for those involved with PET activation. Driven by the need to produce statistically significant results that can accurately localize particular regions in the brain, PET CBF activation data from individual subjects must be added together or superimposed in a process known as intrasubject intramodality coregistration (*10*). Further statistical validity is achieved through combining data from several subjects who have completed the same mental activities. This is known as intersubject intramodality coregistration. Understandably, coregistration techniques must overcome variability between both intrasubject and intersubject data as well as variations from subject positioning. To overcome these variations, many centers use image analysis programs that reformat the combined activation data so that it fits into a standard brain atlas (*20*). This atlas, known as the Talairach atlas, provides three-dimensional coordinate reference points throughout the brain.

While PET activation is able to identify discrete functional areas of the brain, its limited resolution of 6 mm at best, restricts its ability to precisely define structural anatomical locations. Several methods known as intersubject between-modality coregistration have been developed (*19,21*) to reliably superimpose PET data onto MRI data. In our laboratory skull data is removed from MRI images to produce coregistered PET-MRI matched images with Talairach (*20*) coordinates. The colored PET activation data, coregistered with greyscale MRI on a Talairach grid, provides precise cerebral landmarks for the areas of PET activation.

COGNITIVE NEUROPSYCHOLOGY

Cognition, or "the way we think," includes processes such as perception, attention, planning, language, object recognition, memory and mental arithmetic, to name a few (*22*). Research in human cognition has two major disciplines that each use PET activation as a primary research tool.

The central quest of neuropsychology is the nature of the representation of cognition in the brain. Neuropsychology has its roots in behavioral neurology and has always had an interest in the study of individuals with brain impairment (*22*). This is in contrast to cognitive psychology that has a tradition of studying normal subjects to test models of cognition (*23*). The field of cognitive neuropsychology represents a coming together of these two disciplines to increase our understanding of normal cognition by studying cognitive processing in patients with damaged cognition. Cognitive neuropsychology aims to develop explanations for cognitive impairment and to develop therapies for their treatment (*22*).

PET and Cognitive Neuropsychology

Cognitive neuropsychology has used PET to observe the workings of the brain in an array of studies from identifying functional neuroanatomy of human rapid eye movement in sleep and dreaming (*24*) to mapping of brain state during Qigong meditation (*25*). However, most PET activation studies have been completed in language processing, working memory and perception.

Language. Examining relationships between language function and brain structure perhaps has been the main focus of PET activation as a research tool. Two key studies illustrate the basic methodology. In 1988 a group from St. Louis (*16*) designed a two-part paradigm to study areas of the brain responsible for both word repetition and verb generation. The control or reference task in this study required subjects to repeat aloud nouns seen on a computer screen. In the activation task subjects were required to say aloud an associated verb in response to viewing a noun on a screen, (e.g., CAKE → EAT or BEACH → SURFING). This study illustrates nicely the specific PET activation methodology, subtraction, alluded to earlier. The activation during noun repetition was subtracted away from the activation for verb generation. In this way the investigators isolated areas involved in verb generation and separated them from the other stages in noun and verb processing. This study demonstrated that verb generation and noun repetition engage separate and distinct areas of brain anatomy.

Several years later, a group from Hammersmith (*6*) used a paradigm involving four tasks: word reading, hear-and-say, word repetition and see-and-say. In the word reading task, subjects were shown real words on a computer screen and asked to say each word aloud. The word repetition task required subjects to listen to real words on a tape and to repeat each word aloud. In the word reading control task, see-and-say, strings of nonwords were displayed on a computer screen and subjects were required to say aloud the word "crime" as each new string of nonwords appeared. Finally, in the repetition control task, hear-and-say, the word repetition tape was played backwards and subjects were required to say aloud the word "crime" with each new string of sounds.

Howard et al. (*6*), then analyzed the data by systematically subtracting activation for the four tasks from each other to localize several functional areas of the brain responsible for visual and auditory word processing. For instance, by subtracting the see-and-say data from the word reading data, a small area in the left posterior middle temporal gyrus was identified as being responsible for the control of visual word processing. Conversely, an area responsible for auditory word processing in the left superior and middle temporal gyri, close to but slightly anterior to the location of Wernicke's area, was identified by subtraction of the hear-and-say data from the word repetition data (*6*).

Working Memory. Working memory is a short-term component of memory used in holding verbal material in your head. For example, by mentally repeating a telephone number working memory allows us to indefinitely recall the number (*26*). Working memory typically involves a two-stage process: (a) storage of the material as a sound pattern and (b) subvocal rehearsal (*27*). To localize the areas of the brain responsible for working memory, Paulesu et al. (*28*) designed a two-part PET activation study. In the first task, subjects were shown a series of six randomized consonants on a computer screen and asked to repeat and remember the sequence in their heads.

Two seconds after each sequence, a single consonant appeared on the screen and subjects judged if it was in the previous sequence. This task showed that both storage and rehearsal components of working memory were activated in the superior temporal gyri, supramarginal gyri, insulae and bilaterally in Brodman's area. In the second task, single consonants appeared on the screen and subjects were asked to judge if they rhymed with the letter "B." This task was designed to activate only the rehearsal component of working memory and showed bilateral activations in Brodman's area.

Word Retrieval of Concrete Entities. An important issue in the neuroanatomy of language is the location of cerebral areas that are activated when concrete entities, such as people or objects, are recalled and silently verbalized or vocalized (*16*). To investigate this issue Damasio et al. (*29*), using PET activation, showed a series of photographs of famous people, animals and tools to nine normal subjects and asked them to name aloud what they saw on each photograph. In the control activation of this study, subjects were shown a series of unknown faces, displayed either rightside up or upside down, and asked to say "up" or "down." The unknown faces were chosen because they did not trigger a name but did depict real entities. By subtracting away the areas activated by the control task from each of the three activation tasks, this study showed that separate brain regions were responsible for recognizing faces, animals and tools.

Automatic Counting and Calculation. The processing of numbers has been studied by several cognitive psychologists. McCloskey (*30*) postulated a model for explaining the cognitive mechanisms involved in number processing after studying patients with acalculia, an impairment in calculation ability due to acquired brain damage. In the first component of McCloskey's model, numbers, whether Arabic characters or words, are given a basic quantity, such as 100s or 1000s. This leads to the second component–calculating the numerical information, for example comparing two prices for a consumer item to see which is the lesser price or calculating the change from a $100 bill when buying $57.77 of food at a supermarket. The final component involves generating the answer into a suitable output. In the supermarket example, the answer or correct amount of change, $42.23, can either be spoken aloud by the cashier or registered as a number in the mind of the customer. Simple calculation, therefore, requires the use of a notional system, like the Arabic number system, together with arithmetic algorithms, which depend on linguistic competence (*31,32*). It has been suggested that the right and left hemispheres of the brain may be differentially engaged in number as well as language processing, but the question remains unresolved (*33*). To date little work has been reported using PET to study calculation or automatic counting. However, a recent PET study by our group (*34*) comparing simple calculation with automatic counting from one to 20 in normal subjects provided some evidence to confirm McCloskey's (*30*) three-component model for number processing. The data from this PET study showed several discrete areas of the brain were activated during counting. The authors are currently doing a larger study to investigate further the neural networks involved in simple calculation.

PET ACTIVATION AND PARADIGM DESIGN

The preceding overview of PET and cognition makes several references to paradigm design. In PET activation studies a research paradigm, usually involving several well-defined mental processes, must be carefully designed. The data acquired from each mental process or task then can be digitally subtracted from each other to ensure the desired cognitive process is actually being studied. Paradigm design involves the construction of several tasks that result in cognitive activities that are identical except for the individual processes under investigation. For example, in the research paradigm of our study with automatic counting and simple calculation, the first task required subjects to listen to a tape that asked them repeatedly to count aloud from one to 20. In the second task, subjects listened to a tape recording of a series of simple calculations, for example "19 minus 12" or "18 divided by six." The similarities between the two tasks in this paradigm were: listening to a tape, responding aloud to instructions, hearing your own voice and hearing the noise of the air conditioning in the PET room. The difference between these two tasks was automatic counting and calculation. Therefore, subtraction of the activation during calculation from the activation during automatic counting enabled visualization of the areas of the brain responsible for automatic counting and vice versa for simple calculation. Paradigm design must account for anything that causes brain activity including external factors such as room lighting, sound, conversation and visual stimuli (*10*). Anxiety, whether about the PET study, the injection or some other cause also will produce changes in CBF. Familiarizing subjects with the tasks can help reduce anxiety about the study, but the level of practice must be weighed against the possibility of a subject finding the activation task too easy, thus minimizing CBF to the area of interest (*35*). For tasks involving visual stimuli, activity caused by secondary reactions to the stimuli must also be considered. For instance, in a paradigm requiring subjects to recognize the color words "red" and "green," it will be difficult for subjects to think only about the meaning of the words and not about the color of the text if the words are presented randomly on a screen in either "green" or "red" text. This secondary reaction is known as the Stroop effect (*36*). Hence, careful paradigm design is crucial to ensure the activation task actually provides information about the thought or cognitive processes under study.

Illustrations of Paradigm Design: Automatic Counting and Simple Calculation

To provide further practical understanding of the factors involved in PET activation, we will outline some issues from our experience with automatic counting and calculation. In our study we sought to determine where automatic counting and simple calculation occur in the brain. The first step in the design process was to define simple calculation. This included using simple numbers in all calculations and answers, in other words only the numbers one through 20 and only using addition, subtraction and division in the calculations. We reasoned, on the basis of previous research, that producing the answers

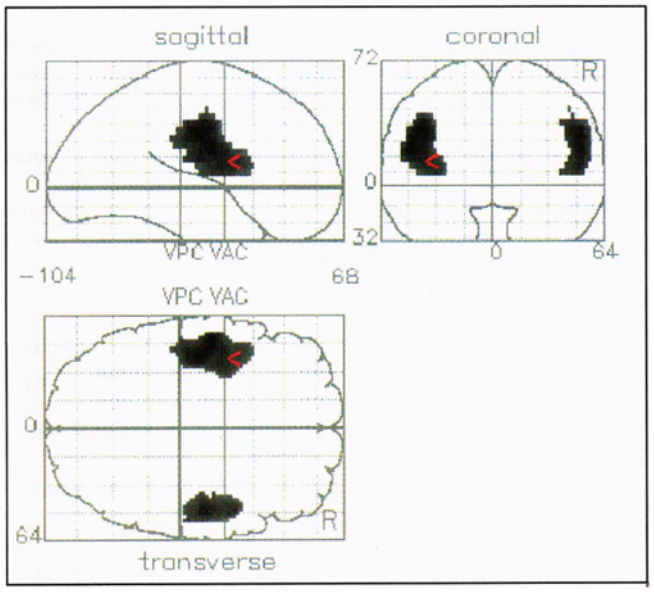

FIGURE 1. Coregistered PET data of automatic counting by four normal subjects. Note how the Talairach grid maps display the PET activation in sagital, coronal and transverse projections.

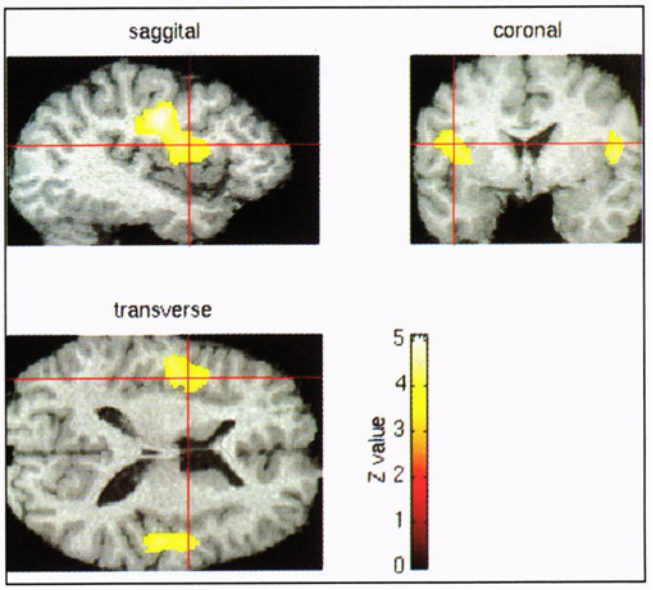

FIGURE 2. Coregistered PET activation data are superimposed onto coregistered MRI data showing the location of automatic counting in both hemispheres of the brain.

to rote-learned multiplication tables would entail less significant cognitive activity. The other part to the paradigm design in this experiment was automatic counting aloud from one to 20. Again this involved listening for instructions, articulating and hearing yourself say the numbers one through 20. We felt that counting these simple numbers was an automatic response that used the same numbers as in the calculation task but did not involve calculation.

Four right-handed male subjects matched for age (mean 23 yr) and level of education were used. The subjects lay in the PET camera gantry restrained in a molded head mask. Room lights were turned off. Each subject had seven 100-sec infusions of $H_2{}^{15}O$, 8 min apart, delivering a total activity of 120 mCi. The short 123-sec half-life means ^{15}O decays to background levels between each infusion. Through a set of small speakers, subjects heard a recorded voice asking a series of simple calculations, such as "20 minus 12" or "17 plus 11." Subjects were asked to say their answers aloud. Under the same conditions as the calculation task, subjects listened to another audiotape and were asked to count aloud from one to 20 at approximately once per second.

The number of incorrect answers was recorded to monitor the level of cognition and the degree of difficulty of the calculations. Although the total study had only four subjects, our two-task, seven runs per subject study provided 28 datasets. These datasets were combined by intersubject intramodality coregistration onto a three-dimensional Talairach atlas shown in Figure 1. Once coregistered, the calculation data were subtracted from the counting data to identify areas in the brain responsible for automatic counting. All subjects had an MRI scan that allowed for intersubject intermodality coregistration of the automatic counting. The colored PET automatic counting data coregistered to MRI in Figure 2 illustrate that counting the numbers one to 20 activates the motor strips of the right and left hemispheres of the brain.

CONCLUSION

PET activation is a powerful research tool through its ability to effectively map functional areas of the brain. We hope this paper heightens professional awareness of PET activation and encourages technologists to develop their knowledge and expertise in this exciting area of research.

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