Toward Clinical Application of Neuropsychological Activation Probes with SPECT: A Spatial Working Memory Task

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The concept of working memory is central to theories of human cognition, because it is essential to human skills such as decision making and deductive reasoning. Although PET and functional MRI have provided robust data on the recruitment of specific pathways in working memory tasks, the experimental settings of these studies may not be transferable to a clinical situation. Hence, to develop neuropsychological SPECT activation probes that are suitable for daily clinical practice, this study reports on a neuropsychological activation task of spatial working memory under classical neuropsychological test conditions in healthy subjects. **Methods:** Reaction times and accuracy were measured as behavioral parameters and functional imaging data were analyzed with statistical parametric mapping to determine significant voxel-wise changes between the perception task and the memory task. **Results:** Subjects reacted more slowly and performed less accurately during the memory task compared with the perception task, findings that are in keeping with other neuropsychological studies. Also, the overall pattern of brain activations revealed in our experiment is consistent with the data of the literature, thereby validating our test probe. **Conclusion:** From a practical viewpoint, the close resemblance of the test conditions of the SPECT procedure with those of the investigation room and the relative simplicity of the task under study probably constitute major advantages for future clinical application of the SPECT procedure in patients with cognitive impairments.

Key Words: neuroactivation probe; working memory; SPECT

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Working memory is a system responsible for the temporary storage and manipulation of cognitive information that allows humans to maintain a limited amount of information in an active state for a brief period of time, at the service of higher-order cognitive functions such as decision making, problem solving, and deductive reasoning (*1*,*2*).

On the basis of neurophysiologic and neuropsychological investigations of nonhuman primates engaged in short-term memory tasks (*3*) and of patients with traumatic brain injury and brain damage due to neurological disease, respectively (*4*,*5*), a prominent psychological model describing the architecture of working memory was postulated by Baddeley in 1986 (*6*). The author proposed a hierarchic model on the composition of cognition, in which the working memory system includes 2 general components: a "central executive" and 2 "slave systems." The central executive is responsible for the coordination of the 2 subsidiary slave systems that have clearly distinct functions and serve as separate material-specific memory buffers, the "visuospatial sketch pad" and the "phonological loop," respectively. Whereas the visuospatial sketch pad is capable of maintaining a limited amount of visuospatial information, the phonological loop stores auditory information for a brief period of time (*7*).

Over the past 15 y, several PET and functional MRI (fMRI) brain studies have not only confirmed Baddeley's concept of cognition by showing how the different components of the working memory system (i.e., storage and executive processes) are implemented in the human brain (*8*–*10*) but also given insight in the temporal dynamics of the activated areas (*11*). These studies used (variants of) item-recognition tasks with either verbal or spatial material while image data were acquired on the PET and MRI camera (*12*). Usually, these procedures consist of a memory task in which several letters or dots are presented on the computer screen, followed by a blank delay period during which subjects have to remember the letters or the locations of the dots, respectively. Next, a probe letter or circle is presented and subjects have to respond whether the letter matched 1 of the target letters or the probe encircled 1 of the target locations (*12*,*13*). Clearly, these tasks necessitate working memory, but include other processes as well (e.g., visual perception and execution of a response). Therefore, to eliminate unwanted activations due to cognitive processes shared by both conditions (*14*), subjects are also engaged in a control "no memory" task. Generally, com-

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parison of the images acquired during the control task with the images acquired during the memory task revealed that in spatial memory tasks activations were in the right hemisphere, whereas activations in verbal item-recognition tasks involved primarily left-hemisphere areas (*15–17*). Moreover, it was indicated that memory was implemented predominantly by the parietal cortex (*13,18*) and executive processes were subserved by prefrontal areas (*19–24*).

Although this research provided us with plentiful and robust evidence of involvement of specific pathways in working memory tasks, these experimental settings may not be transferable to a clinical setting. Therefore, with the aim of developing neuropsychological SPECT activation probes that are suitable not only for research purposes (*25,26*) but also, especially, for clinical evaluation of patients with cognitive impairments, this study reports on a neuropsychological activation task of spatial working memory under classical neuropsychological test conditions in healthy subjects.

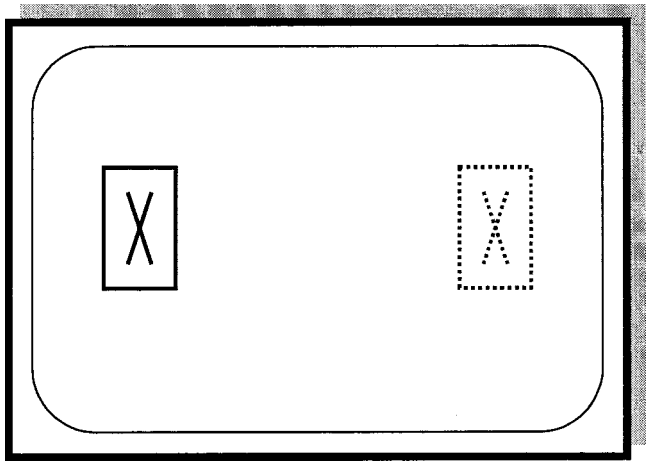

FIGURE 1. Computer screen with target rectangles (stimuli). Solid lines indicate bright-white and dotted lines indicate gray-shaded rectangles on computer screen.

MATERIALS AND METHODS

Subjects

Ten healthy volunteers (8 men, 2 women) with a mean age of 23 y (age range, 20.6–24.5 y) were included in the study. All subjects, except 1, were right-handed as assessed by the Edinburgh Handedness Inventory (*27*) and were Dutch speaking. All subjects had normal vision. None of the participants had a history of major medical, neurologic, or psychiatric disease. Subjects were drug-free with the exception of oral contraceptives. Research was compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Each subject gave informed consent, following the guidelines of the local ethics committee. No subject had any previous experience with the test under study.

Spatial Working Memory Task

Participants performed a control task, further called a perception task, and an experimental activation task, further called a memory task. The perception and the memory task were designed such that they only differed in the involvement of memory effort, which was the process of interest. Subjects sat behind a computer screen (distance, 50 cm; visual angle, 0.8°) with their hands on the computer keyboard and index fingers on marked computer buttons.

In the perception task, subjects were asked to look at brightening stimuli on the screen. Stimuli were rectangles (16 × 7 mm) wherein the letter "X" (2.5 × 3.5 mm) appeared. Two, initially gray-colored, stimuli were presented on a horizontal axis through the middle of the screen, at equal distances from the screen center. During the trial, 1 of the 2 stimuli changed color from gray to white and thus was brightened. Subjects were instructed to push the left-hand button when the left stimulus was brightened and vice versa (Fig. 1). The stimuli were brightened 150 times in a randomized order. Reaction times and accuracy were recorded for 300 successive trials. Subjects viewed a continuous stream of brightening stimuli, each presented for 1,000 ms with a 1,500-ms interval between successive trials (Fig. 1).

In the memory task, presentation of stimuli was likewise. Now, subjects were instructed to press the appropriate button on the keyboard at the moment the next stimulus was presented. Thus, subjects were not allowed to react immediately to the given stimulus but had to delay response until the next stimulus was presented. Therefore, subjects had to remember the site of appearance of a stimulus until the next trial and, hence, had to retain spatial information in the working memory system for a brief period of time. Both tasks equally required perception of the stimuli and motor execution of the response, but they largely differed in the involvement of working memory performance.

To evaluate task performance, accuracy and reaction times were measured. Subjects characterized by behavioral performances of >2 SDs below the mean are excluded from further analysis.

Activation Paradigm Design

The split-dose paradigm was used because it had been shown that a brain flow tracer can be given in a split-dose protocol, enabling at least 1 repeated scan within a short period of time (*28*). The feasibility of this paradigm was demonstrated previously at our laboratory (*25,26*). In accordance with standardized neuropsychological test conditions, subjects were seated at the computer in a quiet room. Subjects were informed about the testing procedure and practicing during a short period of time was allowed to get familiar with the test procedure. Subsequently, a butterfly needle was installed intravenously in the antecubital vein and, after approximately 5–8 min, subjects were instructed to start the perception task. Lights were dimmed and again subjects were allowed to practice, thus ensuring that the motor response was not hindered by the needle. After an additional 30-s period of practice, 555 MBq ^{99m}Tc-ethylcysteinate dimer (ECD) was injected while subjects kept on generating responses for another 270-s period. The injection was performed manually in a bolus over a period of <5 s using a 3-way valve with subsequent flushing with 10 mL saline. After the perception task, image acquisition was performed during a 20-min period. Subsequently, subjects were instructed to start the memory task and the above procedure was repeated. For both the perception task and the memory task, data acquisition started 5–10 min after injection of the tracer. The feasibility of this procedure has been described by Koyama et al. (*29*) (Fig. 2).

Data Acquisition and Reconstruction

Image acquisition was performed with a triple-head gamma camera (model GCA/9300A; Toshiba Medical Systems, Oetwil am See, Switzerland) equipped with low-energy, super-high-resolu-

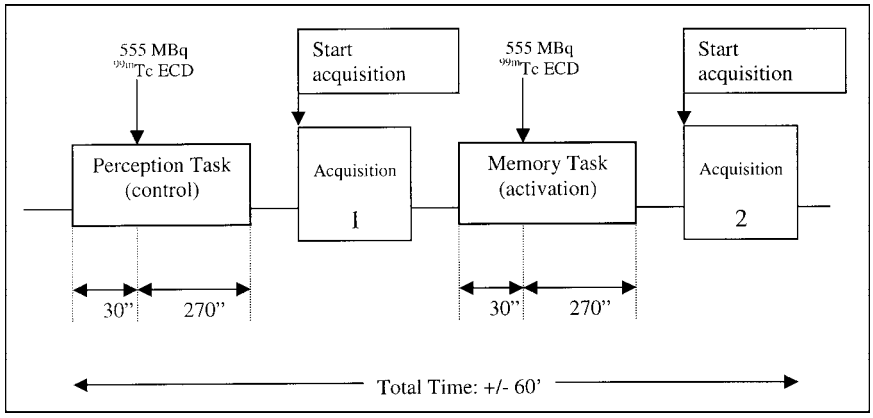

FIGURE 2. Split-dose activation paradigm.

tion fanbeam collimators. The full width at half maximum of this system, as measured in-house, was 7.4 mm for ^{99m}Tc. Triple-energy data for 60 projections were acquired during a 20-min continuous SPECT scan with a 20% main energy window centered around 140 keV and 2 adjacent 7% scatter windows. The resulting pixel size was 1.72 mm. Butterworth filters of order 8 and cutoff frequencies of 0.16 and 0.09 cycle/cm were used for the main energy window and the scatter windows, respectively. Data were scatter corrected using the commercially available triple-energy window method. Scatter-corrected data were subsequently prefiltered with a Butterworth filter of order 8 and cutoff frequency of 0.12 cycle/cm. Image reconstruction was performed with filtered backprojection and a Shepp and Logan filter. Uniform Sorensen attenuation correction was applied with an effective attenuation coefficient of 0.09 cm^{-1}.

Data Analysis

Reconstructed images were converted into Interfile 3.3 format, transferred onto a HERMES processing system (Nuclear Diagnostics, Hagerstad, Sweden) and automatically fitted with BRASS (Nuclear Diagnostics) onto an in-house–constructed template positioned in Talairach coordinates (*30*). The registration procedure used a 9-parameter rigid-body transformation, minimizing a count difference cost function with an iterative downhill-simplex search algorithm (BRASS). Automatically fitted images were converted into ANALYZE format by means of an in-house conversion program (i.e., (X)MedCon). Subsequently, statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, U.K.) was applied to determine significant regions of increased activity. SPM calculations were performed with Matlab 5.3 (MathWorks Inc., Sherborn, MA) on a SUN SPARC 10 computer (Sun Microsystems Europe Inc., Brussels, Belgium). Images were coregistered and realigned, resulting in both registered images and a mean image for each patient. Coregistered images were normalized onto the SPM99 SPECT template. Normalization parameter values were obtained from the mean images. Normalized images were smoothed with an isotropic 12-mm kernel to improve the signal-to-noise ratio. Determination of significant areas of increased activity was obtained using a categoric multisubject, multiple-conditions approach. Mean global activity of each scan was set at 50 mL/min per 100 g. A gray matter threshold of 0.8 and a voxel size of $3 \times 3 \times 3$ mm were used. Statistical comparisons between conditions were performed on a voxel-by-voxel basis using t statistics, generating SPM(t) maps, which were transformed to unit normal distribution SPM(z) maps. We investigated activated brain areas at a height threshold of $P = 0.005$ and an extent threshold of 40 voxels or 1.08 mL. No correction for multiple comparisons was performed because there was a preexisting hypothesis to find activations in the prefrontal cortex.

RESULTS

Behavioral Analysis

The effect of the type of condition (perception and memory) on subsidiary reaction times and accuracy was studied using repeated-measurement ANOVA. Inspection of the data in both conditions revealed that 1 participant exhibited extremely long reaction times in comparison with those of the other participants (average reaction time + >4 SD). The same person showed bad accuracy on the memory task (18% error rate). Therefore, it was decided to regard these results as outlying and exclude the subject from the study.

Reaction times were found to be significantly slower in the memory task compared with the perception task, the mean difference being 124 ms ($P < 0.01$). No effect was documented for the side of the hand used to generate the motor response, nor was an interaction effect between the type of condition and the side of hand used evident.

Comparison of accuracy between conditions (perception and memory) revealed that subjects were less accurate in the memory task compared with the perception task, making almost no errors in the former condition, whereas a 5% error rate was noted in the memory task ($P < 0.005$). Again, no effect was documented for the side of the hand used, nor was an interference effect between the type of condition and the side of hand evident (Table 1).

TABLE 1
Mean Behavioral Responses in Perception and Memory Tasks

	Perception task		Memory task	
Parameter	L hand	R hand	L hand	R hand
Reaction time (ms)	331	344	465	459
Accuracy (% error rate)	0.4	0.6	4.6	5.4

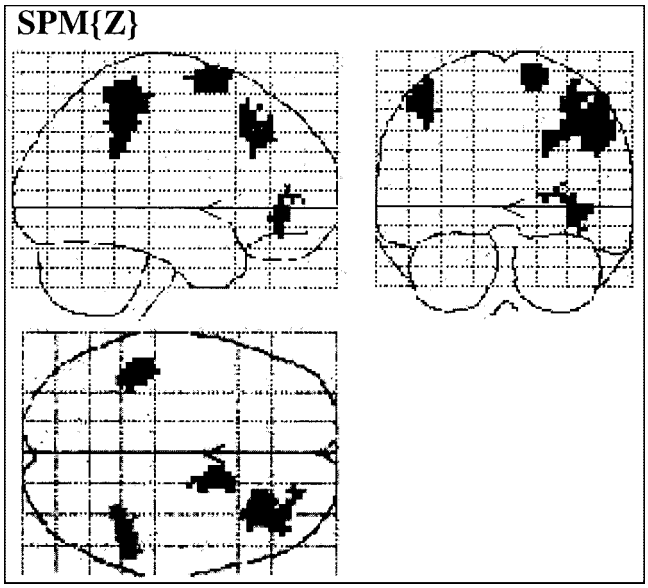

FIGURE 3. Glass-brain images indicate projections of activation clusters in the memory task.

Functional Imaging Results

Comparison of SPECT data of the perception with the memory task by means of SPM showed 5 clusters of activation. Four statistically significant areas of increased activation were located in the right hemisphere and 1 activation cluster was found in the left hemisphere. The first cluster was found in the left inferior parietal cortex (Brodmann area 40; Talairach coordinates = [−45, −36, 57]). There was increased activation as well in the homologous area of the right hemisphere. The second and third clusters were situated in the right prefrontal cortex and comprised the dorsolateral cortex (Brodmann areas 8, 9, and 6; Talairach coordinates = [36, 27, 48], [24, 33, 36], [12, 6, 69]). A final cluster of activation was centered in the inferior part of the frontal lobe in the right hemisphere (Brodmann area 47; Talairach coordinates = [42, 42, −12]) (Fig. 3; Table 2).

DISCUSSION

This study describes a spatial working memory task in which accuracy and reaction times were measured as behavioral parameters, and SPECT activation was performed as a functional imaging technique. For behavioral performance, subjects reacted more slowly and performed less accurately during the memory task compared with that of the perception task. These findings are in keeping with other neuropsychological studies that have indicated that performance gets poorer with increasing memory load (*31*,*32*). To summarize the functional imaging results, the activated brain areas included the right dorsolateral prefrontal cortex, more posterior and inferior regions of the right frontal cortex, and right and left posterior parietal cortex. Thus, the overall pattern of brain activations revealed in our experiment is consistent with the conceptualization of working memory as derived from the above PET and fMRI studies (*13*,*15*) and, therefore, validates the ability of our activation probe to engage neural correlates as used in spatial working memory. All of these areas, except the 1 in the homologous parietal area of the left hemisphere, are concentrated on the right side of the brain. This predominantly right-sided involvement of the brain is consistent with the nonverbal nature of the task and extends previous knowledge indicating that spatial information is processed predominantly by a network of right-hemisphere regions that include well-segregated posterior as well as anterior cortical areas (*15*,*16*). The separate activations in the prefrontal cortex presumably subserve executive functions (*23*,*24*), whereas activations in (bilateral) parietal cortical areas are consistent with involvement of a storage component in memory-demanding conditions (*12*,*13*,*18*). On the other hand, activation of the parietal cortex may also reflect visuospatial attention mechanisms, because an overlap exists between spatial attention and spatial memory (*33*). Moreover, there is current evidence that executive functions resort activation effects in the parietal cortex and storage processes recruit prefrontal areas (*32*,*34*–*36*). Thus, a more distributed view of the cortical organization of the working memory system is suggested, and it is likely that these additional insights account, at least partly, for the activation effects in our study.

Although there may be valid arguments in favor of PET and event-related fMRI procedures from a scientific point of view—in particular, for performing neuroactivation studies (*37*,*38*)—there is also an important drawback when clinical applicability is involved. Usually, PET and fMRI strategies simultaneously perform neuropsychological testing and functional neuroimaging while the patient is lying in a supine position on the camera bed. Consequently, neuropsychological testing is performed in conditions that are not

TABLE 2
SPM: Cluster-Level *P* Values and Activated Brain Regions During Memory Task

Cluster-level $P_{corrected}$ value	Talairach coordinates			Region
	x	*y*	*z*	
0.011	−45	−36	57	L lobulus parietalis inferior (BA 40)
0.027	36	27	48	R gyrus frontalis superior (BA 8)
0.003	24	33	36	R gyrus frontalis medius (BA 9)
0.012	12	6	69	R gyrus frontalis superior (BA 6)
0.000	48	−42	33	L lobulus parietalis inferior (BA 40)
0.002	42	42	−12	R gyrus frontalis inferior (BA 47)

BA = Brodmann area.

comparable with standardized test conditions of sitting at a table or behind a computer screen. Because of this incompatibility of testing the subject in a supine position with the head fixed on the head rest, not only must testing procedures be adjusted to fit the PET or fMRI conditions but also well-validated neuropsychological test results may not be transferable from a standardized test environment to the experimental PET and fMRI settings. Moreover, it may well be that specific brain activations are not related to the nature of the task but (partly) reflect the subject's emotional state caused by the research conditions. Thus, proposing PET and fMRI results, imaging and neuropsychological results alike, as the gold standard may in fact be too presumptuous. On the contrary, the close resemblance of the test conditions of the SPECT procedure with those of the investigation room, and hence the ability of the technique to provide the clinician with validated results, should be regarded as a strong incentive for future clinical application of the SPECT procedure. Obviously, the need to stay as close as possible to the prescribed test conditions is mandatory when diagnostic conclusions in an individual patient are required. So, when using the SPECT paradigm, it may be argued that behavioral and functional imaging results will less likely be influenced by the test conditions than is the case in PET and fMRI studies. Also, in view of future clinical use of the SPECT technique in patients with memory impairments, the choice among many available working memory probes will have to be made in favor of a task that is easy for the investigator to instruct and for the patient to perform. In our opinion, the present task fulfils both requirements.

In this study ^{99m}Tc-ECD is used as a brain perfusion tracer and its characteristics allow freezing of the cognitive state at the moment of extraction of the tracer from the blood. Brain uptake of ^{99m}Tc-ECD takes place pro rata with the microperfusion over approximately a 2-min time window after injection, and subsequent scanning of the subject may be performed until several hours after injection (*39*). As such, through injection of the tracer while the subject is performing a neuropsychological test in standardized conditions, a frozen image of the subject's mental state can be obtained. A single-day, split-dose paradigm was used because it has been shown that a ^{99m}Tc-labeled brain flow tracer can be given in a split-dose protocol enabling at least 1 repeated scan within a short time period (*28*). Also, the choice of a single-day design was inspired mainly by the fact that this protocol, as practiced, is much more comfortable for the patient compared with a 2-d protocol. Importantly, some have argued that within the time frame of a single-day, split-dose brain SPECT activation experiment, the second image acquisition is started at a moment when there is still substantial residual brain activity of the previous injection. Hence, the number of image acquisitions in a single-day ^{99m}Tc brain SPECT activation study is limited to 2. This is in sharp contrast with PET and fMRI activation experiments, which allow not only multiple repeats of the same condition in the same subject, resulting in more powerful conclusions, but also presentation of conditions in reversed order (*40*). Despite these methodologic constraints when using the SPECT technique, our findings are consistent with available data of the literature. Moreover, for clinical use, SPECT imaging of 2 conditions (perception and activation) is sufficient, because comparison of the images acquired in both tasks provides all information that is necessary for the evaluation and follow-up of patients with cognitive impairments. Finally, although no specific medical treatment is available for cognitive dysfunction at this time, verification of the clinical picture with validated neuropsychological and anatomic data may result in individualization of cognitive rehabilitation programs.

CONCLUSION

Single-day, split-dose ^{99m}Tc SPECT allows identification of activated brain regions while the participant is performing a spatial working memory task under standardized neuropsychological test conditions. The main findings, the level of performance and the localization of activation effects in right-hemisphere parietal and (pre)frontal cortical areas, are in keeping with numerous PET and fMRI studies using comparable paradigms. Yet, contrary to the experimental PET and fMRI neuroactivation studies, SPECT more closely approaches the classical neuropsychological test conditions that may constitute the major advantage for future clinical use of the latter technique.

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