◆ **Human Brain Mapping 7:244–253(1999)** ◆

Brain SPECT Imaging and Left Hemispatial Neglect Covaried Using Partial Least Squares: The Sunnybrook Stroke Study

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Abstract: Hemispatial neglect, characterized as failure to attend to contralesional space, is hypothesized by current neuroanatomical models to result from damage to a network involving the frontal, parietal, and cingulate cortices, basal ganglia, and thalamus. This study investigated this model of neglect in 81 right hemisphere-damaged acute stroke patients using 99^{m}Tc-HMPAO single photon emission-computed tomography (SPECT). In order to exploit the inherent collinearity of SPECT regional brain ratios, a novel statistical technique, partial least squares (PLS), was utilized. It makes use of high correlations to identify biologically relevant patterns of brain activity. Averaged ipsilesional cerebellar ratios from 152 brain segments were covaried with performance on subtests of the Sunnybrook Neglect Battery. In this patient sample, the most influential region identified by PLS corresponded to the area surrounding the right temporal-parietal-occipital (TPO) junction that included the right lateral occipital, temporal, and inferior parietal lobes. Hypoperfusion in the medial frontal cortex, including the anterior cingulate, also emerged as significantly associated with more severe neglect. Thus, hypoperfusion in only two of the five hypothesized network regions emerged as significantly associated with hemispatial neglect on SPECT imaging. This work converges with structural imaging studies to suggest that damage to the TPO junction, not just the parietal lobe, may be the critical region for hemispatial neglect. Our study demonstrated the utility of PLS for analyzing functional imaging and behavioral data sets in a clinical population in relation to current neuroanatomical models of neglect. *Hum. Brain Mapping 7:244–253, 1999.* © 1999 **Wiley-Liss, Inc.**

Key words: SPECT; brain; neglect; partial least squares; PLS; stroke

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INTRODUCTION

Hemispatial neglect is typified as failure to orient to contralesional stimuli, when this failure cannot be attributed to either sensory or motor defects [Heilman

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Grant sponsor: Heart and Stroke Foundation of Ontario; Grant sponsor: Ontario Mental Health Foundation.

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Received 18 February 1998; Accepted 10 February 1999

and Valenstein, 1979]. It occurs most frequently following right-hemisphere damage as a failure of patients to attend to stimuli in the left side of space. Although having long been attributed to damage in the right parietal lobe [McFie et al., 1950], neuroimaging studies over the past two decades have suggested that damage to other brain regions may be associated with hemispatial neglect.

Hemispatial neglect can be elicited with a variety of techniques [Schwartz et al., 1997; Coslett et al., 1990; Tegner and Levander, 1991], and different explanations have been theorized ranging from an abnormal internal representation of space [Bisiach et al., 1979] to attentional theories of neglect [Mesulam, 1981, 1990; Heilman et al., 1993]. Extrapersonal neglect, the most common type of neglect, refers to cognizance and interaction that occurs in ''near'' and ''far'' extrapersonal space [Halligan and Marshall, 1991] and can be subdivided into sensory-attentional and motor-intentional systems [Schwartz et al., 1997]. The motor-intentional system mediates overt actions in space, whereas the sensory-attentional system mediates spatial bias. Damage to each system can differentially influence behavioral performance. Although attentional neglect is generally associated with parietal lobe damage and intentional neglect with frontal lobe damage [Heilman et al., 1993; Heilman and Valenstein, 1972], the reverse has also been reported [Ishiai et al., 1994; Triggs et al., 1994]. It has been suggested that both the frontal and parietal lobes function in complementary ways for attentional-intentional processing [Mennemeier et al., 1994]. Further, in our previous study of neglect, in which we experimentally dissociated motor and sensory neglect, we suggested that a common internal spatial representation subserves both perception and action [Behrmann et al., 1995].

A general theory, which incorporates both systems, relates hemispatial neglect to dysfunction in an attentional-arousal system arising from damage to an underlying anatomical network including the frontal, parietal, and anterior cingulate cortices, basal ganglia, and thalamus [Mesulam, 1981, 1990; Heilman et al., 1993]. These three cortical regions have reciprocal connections with each other as well as with the basal ganglia and thalamus. It has been postulated that neglect can occur following damage to either the cortical nodes of the network or the subcortical connections between them, and that its severity will increase in proportion to the number of regions damaged.

Previous localization studies of neglect were based mainly on analysis of subjects with structural damage as demonstrated by computerized tomography (CT) scanning or postmortem examination [Levine et al., 1986; Vallar and Perani, 1986]. With the advent of functional imaging techniques in the 1980s, such as single photon emission-computed tomography (SPECT) and positron emission tomography (PET), examination of the functional disruption of different anatomical regions became possible. With PET or SPECT imaging of brain-damaged subjects, it is possible to investigate function in relation to hemispatial neglect, using metabolism or blood perfusion as an index of brain function and structural damage [Mountz, 1989]. Further, functional mapping can detect functional impairment of structurally intact regions at a remote distance from the primary lesion, a phenomenon called diaschisis [Perani et al., 1988]. Thus, a cerebral blood flow study might be useful in elucidating the functional effects of a lesion and in correlating brain activity in multiple regions of a network with behavior.

With brain imaging data, such as those measured with SPECT, the intercorrelations between brain regions, whether on a pixel-by-pixel or regional basis, commonly involve predictor variables that are highly correlated ($r > 0.8$). Imaging data from patients with stroke, as in this study, may further contribute to highly collinear regions because of brain damage in the territorial supply of occluded arteries. Many functional neuroimaging statistical techniques utilize variations of univariate analyses, and one consequence of collinearity is that statistical analysis can be hampered. For example, classical linear correlation techniques, which are best suited for assessing the contribution of relatively uncorrelated independent predictor variables to a dependent measure, may not be able to find a reliable set of predictor variables, since highly collinear independent variables yield unstable regression equations [Stevens, 1986]. There are multivariate methods that can be used to avoid collinearity issues, such as orthogonal factor extraction using principal component analysis. In this data reduction method, a smaller number of common factors are extracted from a larger set of correlated variables. The factors can then be used in independent comparisons (such as linear regressions or t-tests) and then corrected for multiple tests (Bonferroni-corrected, for example). An alternate approach is to use a multivariate analysis tool such as partial least squares (PLS) that examines the relationships between separate groups of variables simultaneously and emphasizes the relationship between groups of variables.

Partial least squares [McIntosh et al., 1996; Bookstein et al., 1990] is an innovative and powerful multivariate technique that can decompose brain-behavior relationships in large imaging data sets. PLS is a statistical method of data reduction designed to extract linear relationships between two (or more) blocks of variables. In this study, these consisted of brain regions in one block and subtests of a neglect battery in the other. This approach is especially useful when analyzing biological systems. For example, it takes advantage of the inherent redundancy in the brain arising from the parallel functional organization of most anatomical networks. In this study, PLS analysis investigated whether damage in the hypothesized anatomical network, including the frontal, parietal, and anterior cingulate cortices, and the basal ganglia and thalamic nuclei, would be significantly associated with hemispatial neglect. This was tested by covarying neglect scores with mean cerebellar count ratios of different brain regions on SPECT in patients with and without neglect.

METHODS

Population inclusion criteria

The study sample consisted of 81 patients selected from a prospectively studied stroke population admitted to the Acute Stroke Care Unit at Sunnybrook Health Science Centre according to predefined inclusion criteria. Study inclusion criteria specified that patients be right-handed, have at least 20/40 vision with corrective glasses, and have a single, right-hemisphere stroke, supported by CT examination. They also had to be well enough to undergo neglect testing and have a SPECT scan. These criteria yielded a total of 81 patients, 49 with and 32 without neglect.

Sunnybrook Neglect Battery

All patients in the study sample underwent assessment of neglect with the Sunnybrook Neglect Battery (SNB) as part of a standardized clinical stroke protocol. The battery has been described elsewhere [Black et al., 1990; Leibovitch et al., 1998] and comprises four subtests: spontaneous drawing and copying of a clock and daisy, line cancellation, line bisection, and shape cancellation [Weintraub and Mesulam, 1987]. The mean time of test administration was 12.6 days (SD = 13.7 days) poststroke. Psychometric investigation of the Sunnybrook Neglect Battery, based on 232 patients, has shown it to have good internal consistency, with little redundancy of subtests, and good external content validity [Black et al., 1995]. Briefly, all subtests were significantly correlated with the total neglect score ($r > 0.8$, $P < 0.001$) and with each other ($r > 0.5$, $P < 0.001$), thus demonstrating internal consistency within the battery for each individual subtest. Factor analysis revealed that the subtests of the SNB were not redundant, since all four subtests contributed positively to a single factor (eigenvalue = 2.78), which accounted for 69.4% of the variance. Lastly, the SNB was shown to have good external content validity when compared to another test of visuospatial neglect, i.e., the visual search board (VSB) task [Kimura, 1986]. Specifically, logistic regression of the four subtests against the VSB was highly significant ($P < 0.001$).

CT scan procedures

Stroke patients underwent CT scanning of their head on a GE 9800 scanner (General Electric (GE) Medical Systems, Milwaukee, WI) as part of the standard clinical protocol, as detailed in an earlier paper [Leibovitch et al., 1998]. To remove any confounding effect of larger lesion volumes in patients with neglect, since it was expected that patients with neglect would have larger lesions, lesion volume was used as a covariate in the PLS analysis. To obtain structural lesion volumes, lesions were traced from X-ray film onto paper, and the area corresponding to the lesion for each slice was digitized using a Sigma-Scan™ (Jandel Scientific, Corte Madera, CA). The lesion area on each 1-cm-thick slice was summed to arrive at a lesion volume for that scan.

SPECT scan procedures

SPECT scans were generally acquired within the first week of the stroke as part of the standard clinical protocol; specific details of acquisition and reconstruction were detailed in an earlier paper [Leibovitch et al., 1998]. Briefly, scans were acquired on a GE 400 AT single head gamma camera (GE Medical Systems), reconstructed to correct for head tilt in the coronal and transaxial planes, aligned parallel to the orbitomeatal (OM) line, and linearly scaled.

SPECT data used in the PLS analysis were obtained via a previously published [Leibovitch et al., 1998] region-of-interest (ROI) technique that included semiquantitative measurement of the cortical rim and subcortical regions (Fig. 1). Since the SPECT data obtained in this study relate to relative regional blood flow, which cannot be absolutely quantified by the SPECT method, ROIs were also captured in the cerebellum. Dividing by mean counts in the cerebellar reference region standardized mean counts for all segments. Since cortical lesions can give rise to crossed cerebellar diaschisis [Gladstone et al., 1997], which would underestimate cerebellar blood flow, standard

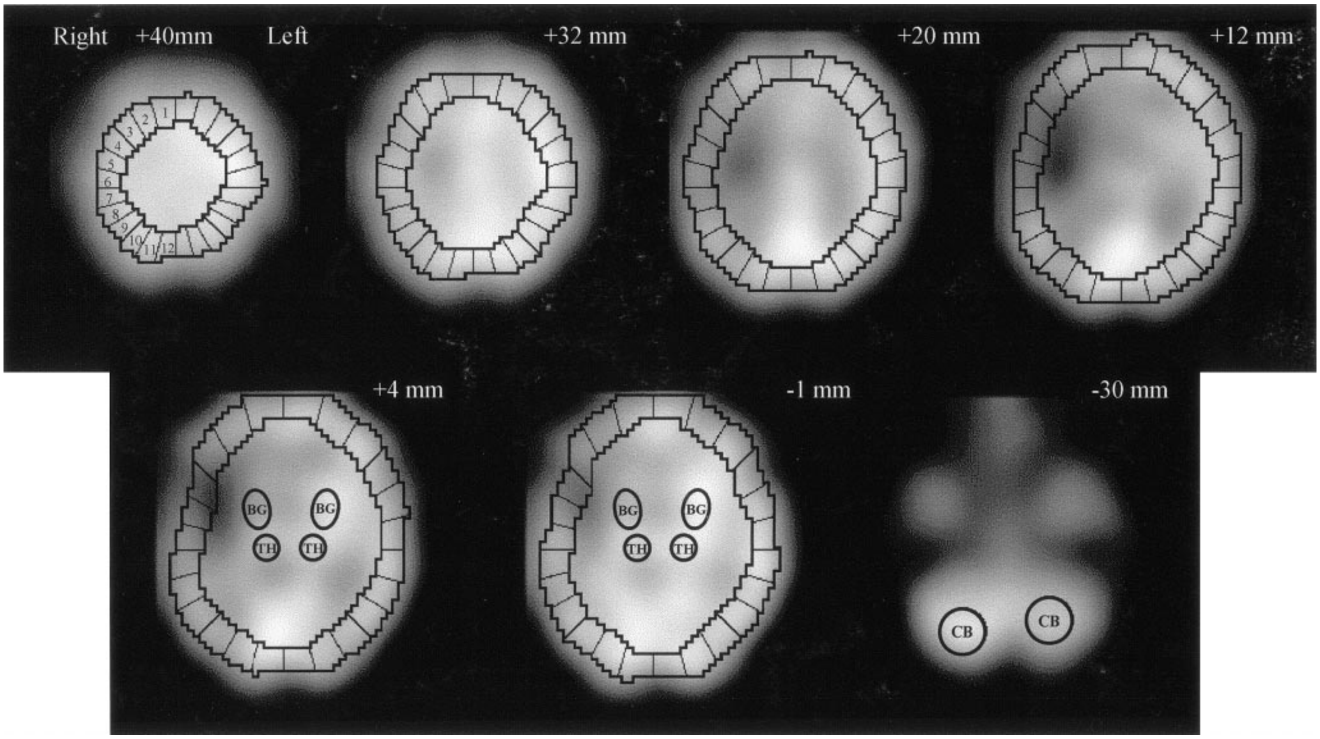

Figure 1.
Semiquantitative SPECT cortical rim and region-of-interest procedure. Numbers around rim refer to individual segments. Numbers in millimeters refer to level above/below AC-PC line corresponding to Talairach slice at that level. BG, basal ganglia; CB, cerebellum; TH, thalamus.

ization was performed using the mean counts from the ipsilesional cerebellum, which should not be significantly affected in this population. One hundred and forty-four cortical rim segments and eight subcortical ROIs were anatomically localized, using a stereotactic atlas [Talairach and Tournoux, 1988]. Thus, 152 individual brain segments were used in the PLS analysis.

Partial least squares

Partial least squares, which was performed using MATLAB software (Mathworks, Inc., MA), operates by decomposing the covariation between two (or more) blocks of data (Fig. 2; for a detailed description of PLS, see McIntosh et al. [1996]). A block corresponds to a two-dimensional matrix of the set of variables of interest (e.g., columns of imaging data (ROI ratios) in which each row corresponds to a patient). To investigate brain-behavior relationships in this study, neglect subtest scores were entered into the *neglect subtest block,* and the 152 segment ratios from the cortical rim and ROI procedure, as described earlier, were entered into the *image data block.* A cross-block correlation matrix, which ignores within-block correlations, is computed and then decomposed into orthogonal dimensions with a mathematical algorithm called singular value decomposition (SVD). SVD computes sets of paired vectors, also referred to as *latent variables* (LVs), that completely reproduce the cross-correlation matrix and relate to the covariance between the blocks. Examination of the resultant LVs delineates patterns of association between the neglect subtest block and the image data block, and thus illustrates the relationship between behavioral and imaging data.

Within each latent variable (i.e., either the vector corresponding to image or neglect battery data) are weights, referred to as *saliences,* that are used to evaluate the influence of different regions. The goal of this method is to determine the relative influences of different brain regions on behavioral performance. The vector corresponding to the imaging data can be remapped into the *singular image* (SI), which summarizes the saliences from the whole data set in relation to the behavioral performance vector for the neglect battery. Examination of the SI for each LV assists identification of the key brain areas associated with the behavioral data.

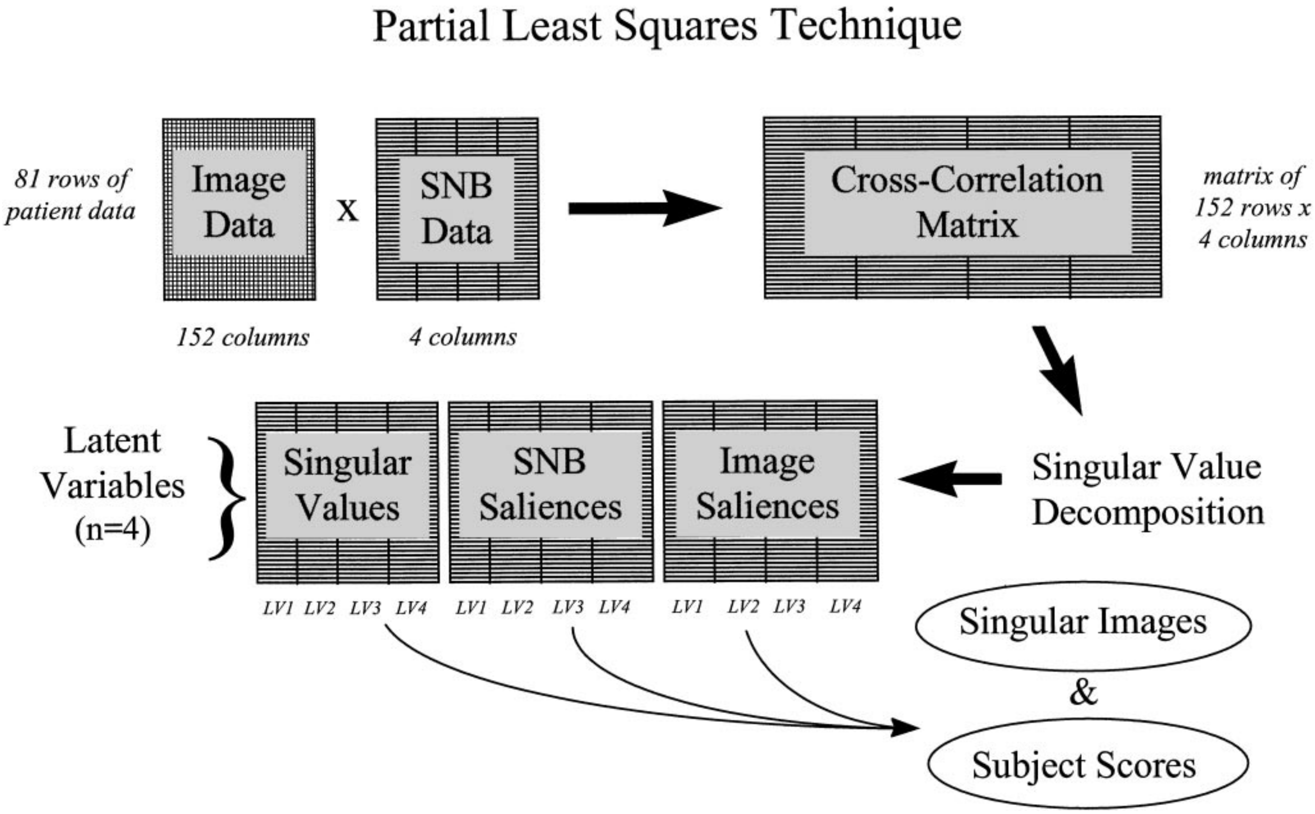

Figure 2.
Diagram of partial least squares (PLS)

By multiplying the saliences from the image vector by the original pixel values (from the original block of imaging data) and then summing across brain regions for each individual, image *scores* can be calculated, such that each subject will have one image score for each latent variable. Similarly, multiplying the vector of subtest saliences by the original subtest score produces a set of subtest scores for the behavioral measure. Both of these scores are then placed in a scatterplot to characterize the relation between blocks for each latent variable generated by the SVD algorithm. The resulting plot is then examined to see if any subgroup differences emerge [Streissguth et al., 1993].

To assess the statistical reliability of the LVs from the PLS analysis, permutation tests [Edgington, 1980; Good, 1994] were performed as follows. The image scores were regressed on the original subtest measures; the squared multiple correlation of this regression (R^2) corresponded to the amount of variance explained by the association between the image and behavioral data and was used as the base value for further comparisons. The rows of the original subtest matrix were then permuted, breaking the association between brain and behavior blocks, and the PLS computation was repeated with different pairings of blocks. The R^2 from the regression of permuted image scores on permuted subtest measures was compared to the original R^2 to determine if the permuted value was as large or larger. The process was repeated 10,000 times, and a probability was assigned to the original R^2 based on the number of times a permuted data set produced an R^2 equal to or larger than the original. In a sense, the test asks the question, "How often does an R^2 value as high as the original occur with any other random pairing of brain and behavior measures?" This question is no different from that asked by conventional parametric statistical tests, but the answer is derived in reference to an empirical permutation of the data rather than a theoretical distribution. As such, assumptions underlying most parametric methods need not be met.

The permutation test assesses the LV structure as a whole, but does not provide an index for which saliences within a LV provide the most reliable or stable contribution. This can be achieved through bootstrap estimation of standard error for the saliences [Efron and Tibshirani, 1986]. To do so, the data are resampled, with replacement, and the PLS performed with the new sample. The standard errors for the saliences are based on the standard deviation for the saliences for a sufficiently large number of resamplings, e.g., 500 in our case. Saliences that were greater than 2.58 times their standard error were considered reliable (a z-score equivalent of a 0.01 level of significance) and provided thresholding criteria for interpretation of the singular images, i.e., for imparting a label of ''significance'' for those saliences. It is important to point out that ''detection'' of an effect is achieved by examination of the LVs for the entire image and is tested through permutation, as explained above. Regional involvement in the detected patterns relates to the issue of ''reliability'' of the effect (and of the corresponding saliences), and bootstrapping is an acceptable method of supplying standard errors for the estimated parameters in a high-dimensional nonlinear analysis [Efron and Tibshirani, 1986].

RESULTS

Population demographics are shown in Table I for patients with and without neglect. As expected, structural lesion volume differed significantly between groups, due to the fact that patients with neglect had larger lesions. To remove the influence of confounding variables prior to PLS analysis, CT lesion volume, age, sex, and education were regressed on neglect subtest scores, and then the calculated residualized scores from the regression analysis were used as the behavioral data in the PLS analysis [Bookstein et al., 1990].

There were four latent variables computed in the PLS analysis, but only the first LV emerged as significant, accounting for 94% of the summed squared cross-block correlation (SSCBC), which provides a measure of the relative influence of the LVs. All four Sunnybrook Neglect Battery subtests contributed equally and positively to this LV. The permutation test for the this LV was significant ($P < 0.05$), with a model that accounted for 41% of the variance explained by the subtests.

Based on the saliences pertaining to the first LV, a singular image was produced (Fig. 3). Calculating the ratio of the salience to its standard error assessed significance of individual segments. Ratios that were greater than 2.58 (a z-score equivalent of a 0.01 level of significance) were considered significant, and segments below that threshold were set to zero for display purposes (Fig. 3). Interpretation of the latent variables requires knowledge of the relationship between the imaging and subtest saliences. For example, a negative imaging salience and a positive subtest salience mean that higher scores on the subtest battery will be associated with lower blood flow ratios. The most negatively salient regions included the right lateral occipital, inferior parietal, and temporal cortices (Brodmann's areas 18, 19, 21, 22, 37, 39, and 40). The right medial frontal cortices (Brodmann's areas 9, 10, 24, and 32) also emerged as significant.

TABLE I. Population demographics summary

Group	No neglect (n = 32)	Neglect (n = 49)	Significance between groups
Age (years)	68 ± 13*	72 ± 11	n.s.**
Gender	18 males 14 females	25 males 24 females	n.s.
Education (years)	12 ± 4	13 ± 5	n.s.
CT lesion volume (in cm^3)	19 ± 38	58 ± 69	$P < 0.005$

* Mean ± standard deviation.

** Significance on univariate tests between neglect groups. n.s. = not significant.

The image and subtest scores for the first latent variable were placed in a scatterplot to visualize the relation and to see if any patterns emerged (Fig. 4). The advantage of this visual approach is that it facilitates identification of specific relationships within the PLS output by graphically portraying the data. Figure 4 shows a relatively clear separation between patients with and without neglect, especially for patients with more severe neglect, which is the group of patients in Figure 4 at right. However, no specific neglect subgroup differences were revealed.

DISCUSSION

As far as we are aware, this is the first large group study of brain-behavior correlations in left hemispatial neglect using SPECT imaging. This study is also original in using the partial least squares technique in a large clinical population to covary imaging and behavioral data. The functional results from the PLS analysis of the SPECT data revealed a strong relationship between decreased perfusion in the right inferior parietal, lateral occipital, and temporal cortical regions, and an increased score in the four subtests of the Sunnybrook Neglect Battery. In addition, a smaller significant relationship also emerged between the right medial frontal cortex that included the anterior cingulate cortex. The results, however, did not confirm involvement of all regions of the theoretical network underlying hemispatial neglect [Mesulam, 1981, 1990; Heilman et al., 1993], which is composed of three cortical and two subcortical regions.

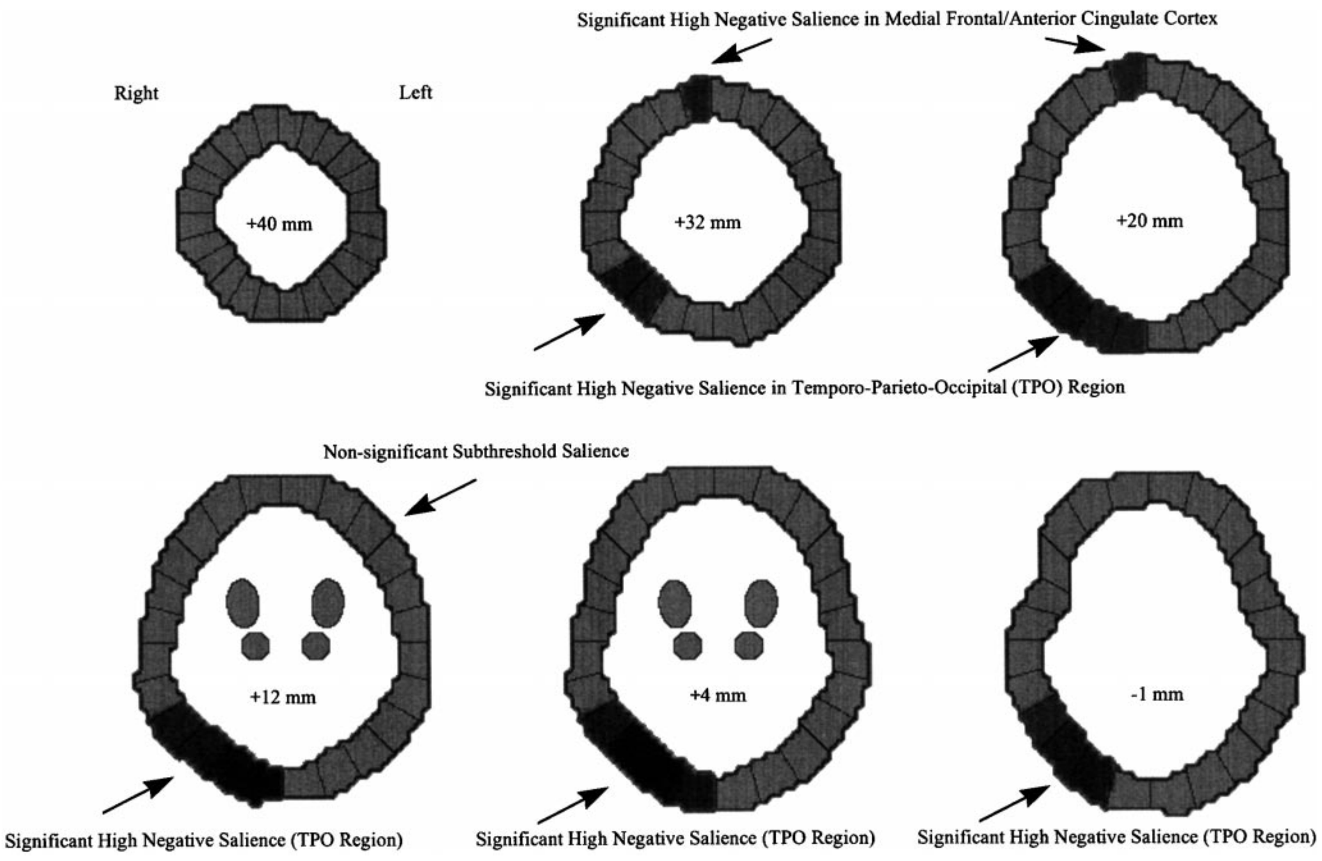

Figure 3.
Singular image for the first latent variable. Regions with significant high negative saliences appear black, and segments with nonsignificant subthreshold saliences appear gray. Significance refers to segments whose salience/standard error is greater than 2.58 (i.e., $P < 0.01$). Numbers in millimeters refer to level above/below AC-PC line corresponding to Talairach slice at that level.

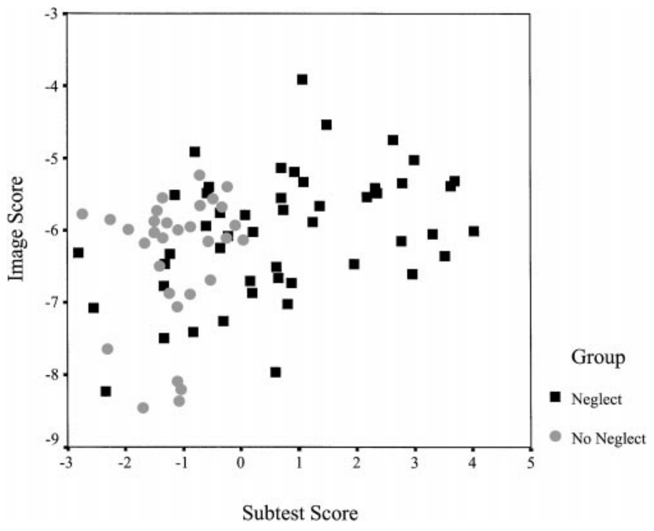

Figure 4.
Image vs. subtest scores for the first latent variable.

From the PLS analysis of the imaging data, the right lateral occipital and temporal cortices emerged as associated with the subtests of the Sunnybrook Neglect Battery. One reason that these regions emerged was that the bedside tests used to elicit neglect are primarily visuoconstructive in nature. For example, our battery required drawing of objects, placing centering marks on lines, and detection of lines on a page and of targets from an array of foils. Such tasks are likely to depend in part on the integrity of the visual association cortices [Goodale and Milner, 1992; Ungerleider and Mishkin, 1982] and the ventral occipitotemporal visual projection system [Mishkin et al., 1983].

Although the anatomical model of neglect does not directly implicate these regions, this finding was not surprising, since these regions border on the temporal-parietal-occipital (TPO) junction, a region previously noted to be important in neglect [Vallar and Perani, 1986]. In fact, the most important area that emerged overall in the PLS analysis was the inferior posterolateral cortex, surrounding the TPO junction. The fiber bundles deep in the TPO junction contain association fiber tracts critically interconnecting the lobar regions, locally [Pandya and Yeterian, 1990], anterior-posteriorly [Seltzer and Pandya, 1984], and interhemispherically [Dobkin et al., 1989]. Damage to this area would affect both nearby areas, such as the parietal lobe, and distant areas, such as the frontal lobe. In humans, the TPO junction has connections with the visual, tactile, and auditory unimodal sensory association areas and is considered to be a polymodal sensory region. The fact that these areas covaried negatively with neglect score provides empirical support for the important role of these posterior regions in hemispatial neglect. This finding is consistent with a previous group study that showed that left hemispatial neglect was associated with right posterior lesions and not anterior damage [Vallar and Perani, 1986]. It is also convergent with our recent study, which provided empirical evidence that the white-matter fiber tracts passing through the TPO region, including the posterior superior and inferior longitudinal fasciculi, were significantly more damaged in patients with neglect than without [Leibovitch et al., 1998].

The right parietal region, specifically the inferior parietal, also emerged as significantly related with hemispatial neglect as measured by the Sunnybrook Neglect Battery. This finding conforms to expectations from the clinical literature. The parietal cortex has been implicated in hemispatial neglect since the earliest clinicopathological correlations [Brain, 1941]. However, the recognition from single-case reports that neglect can occur with damage elsewhere and the proposed theoretical anatomical network [Mesulam, 1981, 1990; Heilman et al., 1993, 1994], which emphasizes neural connectivities, tended to deemphasize the role of the parietal region and imply that all nodes were equally important. Our data reaffirm the primacy of damage in posterior brain regions, including multimodal parietotemporal association cortices as well as visual association cortices, and these data are convergent with a CT analysis of lesion localization in this same population from our unit [Leibovitch et al., 1998], and with one other large group CT localization study [Vallar and Perani, 1986].

The only anterior region to emerge reliably from the PLS analysis was in the medial frontal cortex. This region consisted of segments near the frontal pole that also contained pixels from the anterior cingulate cortex. Although the significant segments were contained within the frontal lobe, they were at a distance from the frontal eye fields, the specific frontal region outlined by Mesulam [1981, 1990]. Thus in this analysis, the anterior cingulate but not the frontal eye fields emerged as being significantly associated with hemispatial neglect, as measured by the Sunnybrook Neglect Battery.

The two other regions in the model that were not significantly associated with neglect were the basal ganglia and thalamus. These regions may not have emerged because they are commonly affected in middle cerebral artery territory strokes irrespective of neglect behavior, and may be damaged equally in patients with and without neglect. A second reason may be that adjacent interconnected regions were able to compensate for the loss of functioning in these regions [Grady, 1996], whereas compensation for the parietal lobe may have been insufficient.

Although these regions did not emerge from the PLS analysis, this does not of course mean that they are not involved in the anatomical network for directed attention. The functional imaging data for this study were derived in the resting state from patients with acute, acquired brain damage, whose functional network was disrupted. The fact that a region did not emerge in our analyses cannot exclude the possibility that those regions are involved in a normally functioning brain. Recent studies by Gitelman et al. [1996] and Nobre et al. [1996] provided supporting evidence for the postulated cortical network for directed attention in the normally behaving adult human. Using functional magnetic resonance imaging (fMRI) in normal subjects, they showed that the frontal, parietal, and cingulate cortices were activated in tasks requiring directed attention and spatial orientation. Similarly, Corbetta et al. [1993] provided evidence from PET that areas within the superior parietal and frontal regions differentially activate, depending on the requirement of the task (spatial vs. directional). The results from the current study reflect functional lesion localization in hemispatial neglect. Using such lesion data, inferences may be drawn about regions which, when damaged, disrupt normal function. The "control" population in this study was composed of acute stroke patients who did not display neglect. Thus, brain regions that were not differentially associated with hemispatial neglect may not have emerged as a result of the fact that those regions were damaged in both groups. The fact that a region does not emerge in such an analysis suggests it may not be critical for this function, but does not speak to the potential involvement of that region in normal function. Studies based on the lesion method are best used in conjunction with normative studies now possible with noninvasive functional neuroimaging techniques. Normative studies can reveal which brain areas are activated during cognitive tasks. Lesion studies can reveal which of these areas may be critical for these functions, i.e., may allow inferences regarding the relative importance of these regions, which cannot be inferred from the normative data.

CONCLUSIONS

This study used a novel statistical technique, i.e., partial least squares, to test the hypothesis that the neural correlates of hemispatial neglect involve a network of anatomical regions including the frontal, parietal, and anterior cingulate cortices, basal ganglia, and thalamus. The regions of this network that emerged significantly on SPECT were those surrounding the right temporo-parieto-occipital junction, including not only the right inferior parietal cortex, but also the lateral occipital and temporal cortices, and the anterior cingulate region. Hence, this study emphasizes the importance of the posterior multimodal association cortex in hemispatial neglect. It has shown the value of covarying a functional imaging technique, such as SPECT, with a neuropsychological assessment of spatial attention in patients with hemispatial neglect to elucidate brain-behavior relationships. Finally, it has demonstrated the utility of PLS for analyzing complex functional imaging and behavioral data sets to test current neuroanatomical models of neglect.

ACKNOWLEDGMENTS

The authors thank Drs. J.R. Wherrett, M.-P. McAndrews, F.S. Prato, M.-L. Smith, G. Winocur, S. Kohler, and C. Szekely for their comments on the M.Sc. thesis upon which this work was based. We also thank K. Ma for helping with the SPECT data; J. Lawrence, N. Blair, J. Bondar, and D. Martin for collecting the behavioral data; our neurological colleagues Drs. J. Edmeads and A. McLean and the technologists of the department of Nuclear Medicine at Sunnybrook Health Science Centre, Toronto, ON, Canada for their assistance.

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