Display of Fused Images: Methods, Interpretation, and Diagnostic Improvements

Rik Stokking, I. George Zubal, and Max A. Viergever

The use of integrated visualization for medical images aims at assisting clinicians in the difficult task of mentally translating and integrating medical image data from multiple sources into a three-dimensional (3D) representation of the patient. This interpretation of the enormous amount and complexity of contemporary, multiparameter, and multimodal image data demands efficient methods for integrated presentation. This article reviews methods for fused display with the main focus on integration of functional with anatomical images. First, an overview of integrated two-dimensional (2D) and 3D medical image display techniques is presented, and topics related to the interpretation of the integrated images are discussed. Then we address the key issue for clinical acceptance, ie, whether these novel visualization techniques lead to diagnostic improvements. Methods for fused display appear to be powerful tools to assist the clinician in the retrieval of relevant information from multivariate medical image data. Evaluation of the different methods for fused display indicates that the diagnostic process improves, notably as concerns the anatomical localization (typically of functional processes), the registration procedure, enhancement of signal, and efficiency of information presentation (which increases speed of interpretation and comprehension). Consequently, fused display improves communication with referring specialists, increases confidence in the observations, and facilitates the intra- and intersubject comparison of a large part of the data from the different sources, thereby simplifying the extraction of additional, valuable information. In most diagnostic tasks the clinician is served best by providing several (interactive and flexible) 2D and 3D methods for fused display for a thorough assessment of the wealth of image information from multiple sources.

CLINICIANS ARE FACED with an enormous increase of information caused by the rapid developments in three-dimensional (3D) imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), single photon emission computed tomography (SPECT), and positron emission tomography (PET). It is to be expected that the amount and complexity of the data will continue to rise at a steady pace because of the increase in spatial and temporal resolution of current scanners, but also by the advent of new (and more complex) imaging modalities. The mental integration of all these data into a 3D representation is very difficult, and the clinician will need more and more assistance in interpreting and integrating information from the different sources.

Computer-aided techniques are required to assist the clinician in integrating the image data. Clinical applications that profit from integration are the display of CT and MR images with electromagnetic dipole data for neurosurgery,[1] presentation of CT/ MRI data combined with dose distributions for radiotherapy planning,[2] and integrated visualization of SPECT and MR brain image data to investigate tumor related perfusion changes.[3] Integration involves two fundamental stages, ie, the registration or matching of the data from the different sources and the visualization or display of the registered data. In this article we mainly focus on visualization methods to combine functional (SPECT, PET, functional MRI [fMRI]) with anatomical images (CT, MRI). Functional images are inherently hampered by their low spatial resolution,[4,5] and integration with anatomical data may aid in the analysis of the functional information.[6-8]

Another important emphasis of this review is on the structure being imaged. So far, most of the research in the area of integrated visualization has been devoted to the brain. The reason is that high registration accuracy can be achieved because the brain is enclosed by a rigid structure, ie, the skull. Registration in other parts of the body is much more difficult because of problems caused by motion (respiration, bowel, cardiac, etc.). This review consists of two major sections: (1) a description of methods for integrated 2D and 3D visualization and a discussion of issues related to interpretation of the resulting fused images and (2) an overview of the possible diagnostic improvements obtained when applying these methods.

METHODS FOR INTEGRATED VISUALIZATION AND INTERPRETATION OF THE FUSED IMAGES

Integrated 2D Visualization

Adjacent display of 2D images from different sources on a light-box or computer screen can be considered the

---

From the Departments of Radiology and Medical Informatics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; Diagnostic Radiology Yale University Medical School, New Haven, CT; and Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands.

Address reprint requests to Dr. R. Stokking, Medical Informatics and Radiology, Ee2167, Dr. Molewaterplein 50, Erasmus MC, University Medical Center Rotterdam, 3015 GE Rotterdam, The Netherlands.

This research was funded in part by the National Institutes of Health, Grant No. R01-S35674.

0001-2998/03/3303-0015$30.00/0
doi:10.1053/snuc.2003.127311

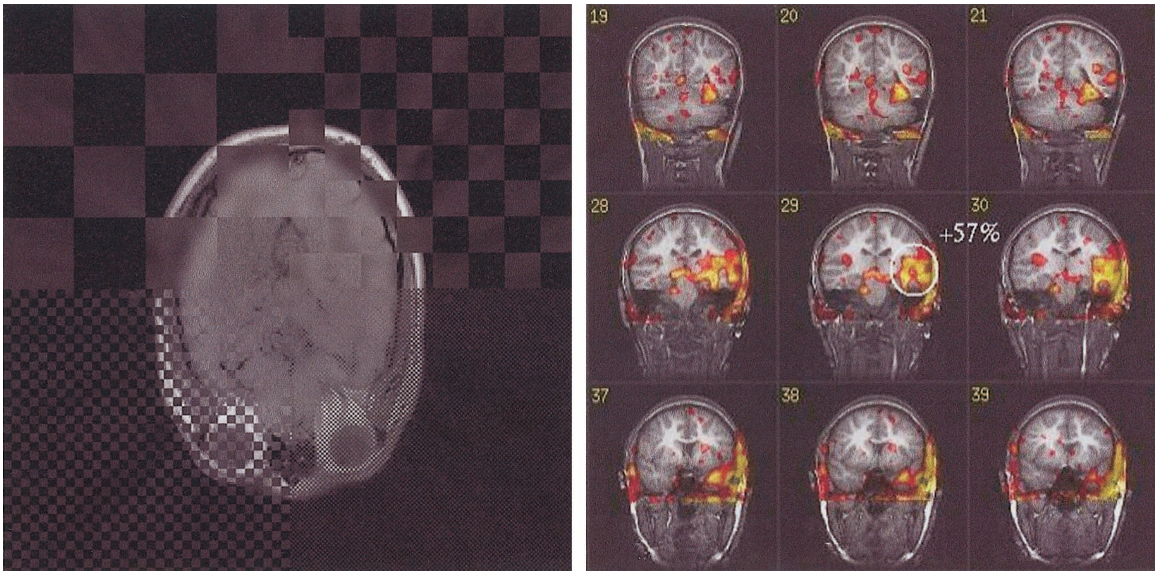

Fig 1. **2D fused display. (Left) Checkerboard display of an MR and a SPECT image. The size of the checkers goes from large (left top) to small (right bottom). (Right) Color fusion display of SPECT perfusion increases during a seizure combined with the corresponding MR images for an epileptic patient with a focus in the left temporal lobe.**

most elementary form of fused display. A valuable extension is the addition of a linked cursor to mark analogous positions in a number of images.[9-21] However, these methods of integrated display still leave the observer with the mental integration of the information, because, technically, the information from the different sources is not combined into one (or more) image(s).

True integrated display of multiparameter or multimodal information is when the image information from the different sources is combined into one (or more) image(s). Two categories can be distinguished for this combined display of information:[3,7,9,22,23]

Nonselective Integration

Information from different images can be integrated using simple methods, such as multiplication, addition, or color combination, thereby combining all information into one image. Although these techniques are easy to use and enable quick presentation, they are usually not very effective. The danger with most of these techniques can be that relevant information is camouflaged by irrelevant data, thereby degrading the diagnostic quality of the integrated display (see also Rehm et al[24] and Quarantelli et al[25]). This may not be a problem when assessing registration accuracy for research purposes, but may well hamper clinical observation tasks. An exception is the use of color models [11-14,17,21,26-42] because the human visual system employs color more effectively than it does gray levels.[26,43] One of the main problems with color fusion used to be the limited color display capabilities of monitors,[28,29] but nowadays 24-bit (or true color) monitors are widely available, and this has considerably alleviated the application of color fusion for integrated display. Several options for color fusion can be applied, eg, independent use of the red-green-blue (RGB) or hue-saturation-value (HSV) components, or averaging or multiplication of the color components when combining two or more images. For example, the so-called colorwash technique[44] can be used whereby a pseudocolor image is added to a greyscale image. Others have applied the HSV model to keep the sources of information separate, eg, for the combined visualization of MR images (encoded in the value component) and SPECT information (encoded in the hue and/or the saturation component).[3,45] This clear separation makes HSV a highly suitable color model to allow easy, rapid, and intuitive retrospective manipulation of the color encoding of an integrated display.

The so-called checkerboard display[13,16,19,24,34,46-49] (see Fig 1, left frame) may also be considered a type of non-selective fused display. The technique is primarily used to simulate some sort of transparency effect or to present and to verify registration results in technical research articles. The effectiveness of this display for verification of registration accuracy in a clinical setting is probably limited because typically half of all the information, whether relevant or not, is removed, and interpretation is mainly limited to the borders of the checkers. Furthermore, perceptual problems have been reported most notably when the size of the checkers is small (eg, size of 1 pixel) and when color is used (see also Hawkes et al[9] and Rehm et al[24]).

Selective Integration

Selective integration is the segmentation of characteristic diagnostic aspects (eg, regions, object boundaries, intensity ranges) whereupon these aspects are integrated into the display of another modality.[10,13,15-18,27,38,40,42,44,46,50-63] This integration aims to present a more efficient display of the data by conveying only the relevant information needed for the diagnostic task and by minimizing the obstruction of relevant data from the other source. Typically, relevant information is segmented from anatomical data, eg, contours (automatically) extracted from MR brain images overlayed onto PET slices, or a range of functional data (usually the higher values) is color encoded and replaces anatomical data.

In the literature, virtually all 2D integrated visualizations either use non-selective integration employing color models or selective integration. In addition, the mixed use of these methods is popular, eg, color fusing a range of functional data with anatomical information[14,64-68] (see Fig 1, right frame). One of the major drawbacks of all 2D display techniques is the inherent inability to visualize in three dimensions, which leaves the observer with the task of mentally translating a 3D representation from the 2D slice data. To assist the clinician in this difficult translation task, several volume visualization techniques can be applied to produce a 3D representation of one or more objects.

Integrated 3D Visualization

Methods for integrated 3D visualization can be divided into several categories:

Linked Feature Display

This type of integrated 3D display is a logical extension of the aforementioned 2D linked cursor. A linked cursor (or any given object such as points, lines, planes, etc.) can be used to indicate a location or a set of locations in a 3D volume visualization and its corresponding location(s) in another (2D and/or 3D) image from a different source.[6,69]

Integrated Data Display

Segmentation of objects in one data set allows the subsequent integration into another data set whereupon standard 3D rendering methods[70] can be used to obtain an integrated 3D display. Typically, the focus is on the visualization of segmented tissues and/or abnormalities[2,13,32,40,55,60,64,71-76] by using opaque or transparent surfaces[7,74] or points and contours as single or multicolor overlays.[77]

Multimodal Window Display

Substitution of a section of a volume rendering of a source data set by the corresponding section of a volume rendering of another source data set is called multimodal window display. For example, a part of a brain visualization from an MRI can be substituted with the corresponding maximum intensity projection from SPECT data to allow the analysis of the functional information in an anatomical framework. Once the two volume visualizations are available the window display can be very fast, allowing interactive manipulation of the window size and location. The main difficulty with multimodal window display is the problem associated with volume visualization of the functional information. Functional volume data acquired using sources such as SPECT or PET are inherently difficult to render, and this hampers the corresponding multimodal window visualization. In spite of this problem, multimodal windows have been applied, eg, for MRI/PET,[6] MRI/CT,[71] and MRI/SPECT.[3]

Multimodal Cutplane

The established use of cutplanes (see Fig 2, left frame) in volume visualization indicates that it is a powerful method for the analysis of image data. Essentially a cutplane is a 2D image within a 3D visualization, which means that all previously discussed methods for 2D fused display can be applied to integrate information on the cutplane. Consequently, the resulting image allows close investigation of the (functional and/or anatomical) information on the multimodal cutplane presented in an anatomical frame of reference, eg, supplied by a volume rendering of the brain.[76] Several typical examples of multimodal cutplanes can be found in three articles: (1) a 3D visualization of the skull from CT and skin from MRI, with two cutplanes showing the original MRI and CT greyvalue data,[78] (2) a volume rendering of the brain from MRI with a cutplane representing functional information,[79] and (3) a volume visualization of the brain from MRI with functional information combined with features extracted from anatomical data.[3]

Surface Mapping, Texturing, or Painting

Information from one source can be mapped and (color) encoded onto the surface derived from another image data set. Typically these techniques are applied to target brain data, usually mapping, texturing, or painting functional information onto the surface of the brain. Texture mapping can be employed to integrate functional data onto the surface,[79] but this technique will only show a small portion of the relevant data, ie, the functional information at the defined surface, in the resulting image. Valentino et al[80] proposed a method whereby a neighborhood of functional data is first mapped onto an anatomical volume whereupon the combined data set is rendered. Because most of the mapping techniques target the brain, more specifically the gray matter, several methods were devised to map the underlying functional data onto the cortical surface.

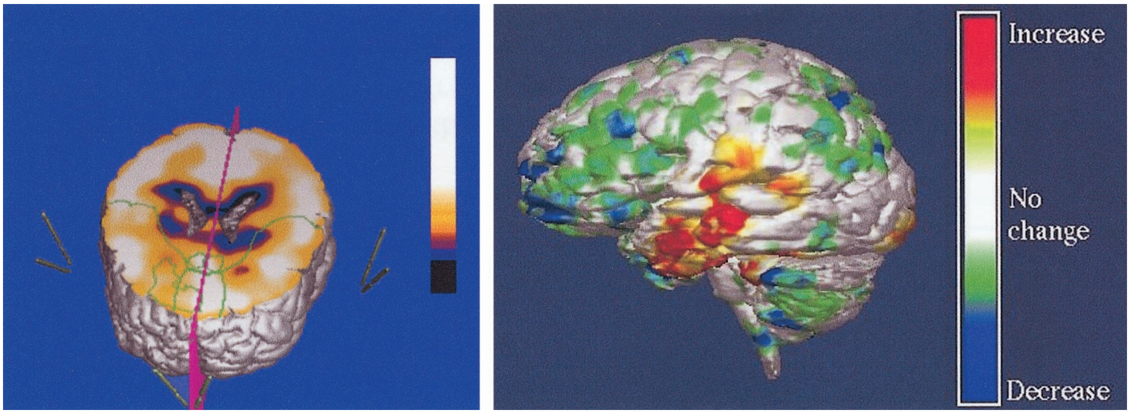

Fig 2. 3D fused display. (Left) Multimodal cutplane combining color encoded SPECT information with features segmented from MR data. The cutplane is presented within a 3D visualization of the brain segmented from MRI. The green tubes are the three V-shaped markers that were used for the registration of the data. (Right) Normal Fusion visualization of SPECT difference data color encoded onto the brain segmented from MRI, same patient as in Fig 1 right frame.

Sampling and mapping the functional activity below the surface along a trajectory determined by the viewing direction of the volume visualization was proposed by Levin et al[6] However, integration along this viewing trajectory generates uncertainties in the location of the mapped information as a formidable portion of the functional data will be fused onto the incorrect surface area, eg, the neighboring gyrus. To overcome this problem, the Normal Fusion technique was proposed, which allows sampling and mapping along a trajectory perpendicular to the local surface. When applied to, eg, the cortex, Normal Fusion assures that the functional data are mapped and color encoded onto the anatomically correct gyrus and results in a 3D integrated visualization that is independent of the viewing angle.[81] Normal Fusion has been used for fused (brain) displays for functional and anatomical information, ie, (difference) SPECT with MRI[81-84] (see Fig 2, right frame), PET/SPECT ratio-images with MRI,[85] PET with MRI,[45,86] and fMRI with MRI.[45] Color encoding in Normal Fusion is based on the HSV color model, ie, shading of the anatomical surface yields the value component and the mapped functional data are color encoded through the hue and saturation components of the corresponding surface element. The HSV color encoding strategy allows easy, rapid, and interactive manipulation of the color encoding of the functional information in the integrated visualization, which was greatly appreciated by the clinicians.[45]

Complementary Visualization Techniques

The aforementioned techniques for 3D integrated display can be augmented using standard presentation methods, such as movie sequences and stereo display, for an improved 3D perception. Furthermore, several methods have been proposed to flatten or unfold surfaces to allow investigation of (a major part of or) the whole surface in one image. Not only are fewer images required, but relationships are easier to assess, eg, when comparing the left and right hemisphere of the brain. Examples of fused displays in this context are the combination of electroencephalogram (EEG) activity with an unfolded cortex extracted from MR image data[87] and the presentation of SPECT information fused onto the unfolded brain extracted from MRI.[88] The interpretation of the images obtained using these unfolding/flattening methods typically requires minimal training to relate the unfolded surface to its true 3D anatomy.

DIAGNOSTIC IMPROVEMENTS

Clinical acceptance of methods for fused display follows from the key question whether these methods can improve the diagnostic process in some way. A wealth of articles discuss diagnostic improvements following the use of integrated visualization. The following separation of the diagnostic improvements aims to categorize the articles, but the separation is difficult (and inherently arbitrary) because certain categories overlap.

Anatomical Localization

Virtually all articles listed in this review point out that fused display improves anatomical localization, which indicates that it is the principal reason for fused display. Especially in combining functional and anatomical data, the latter provides the localizing framework for the functional information, which is typically hampered by a low spatial resolution (for the importance of the additional anatomical information, see also Drevets et al[12]). Furthermore, the quantification of functional data of specific regions of the body is considerably improved and is less subjective when a region or volume of interest, which was segmented from the corresponding anatomical data, is used.

A multi-observer study specifically evaluated four types of fused display for anatomical localization of functional brain data.[89] The task was to localize cold and hot-spots in the peripheral cortex of the brain with respect to lobes and gyri. SPECT and MRI data of 30 patients were presented using either (1) 2D SPECT display, (2) adjacent display of (2D) SPECT images with corresponding MRI slices, (3) integrated 2D display of SPECT images with superimposed contours from MRI, and (4) integrated 3D display (Normal Fusion images). The integrated 2D display modes (2 and 3) resulted in an increase of the agreement among raters in their localizations compared with the 2D SPECT display (1). A further increase was obtained when using integrated 3D display (4).

Registration

Fused Display for Interactive Registration

Several methods have been presented where integrated visualizations are part of a tool to register data sets from different sources by interactive manipulation of the data. The so-called hat-head method of Pelizzari et al[22] is an automatic technique to find the best match between (segmented) surfaces from different sources of information. During this process the user is continuously presented with updated contours and points indicating the surfaces and allowed to interrupt and modify parameters to speed convergence to the optimal surface match. Pietrzyk et al[90,91] used fused displays (contours from MR overlayed onto PET slices and color wash to fuse 2D MR and PET images) so that the user could translate and rotate the data to find the best visual match. Kapouleas et al[51] discussed a method where the user is first required to identify landmarks in two data sets to align the interhemispheric fissure. Then the user is presented with automatically extracted contours from MR overlayed onto PET slices and allowed to interactively rotate and translate the contours to calculate the best match. Soltys et al[38] presented an interactive registration method and provided the user with an array of fused displays to choose from. The authors of these studies found that gross misregistration is best handled by 3D views of the data, whereas arbitrary cutplanes are the most useful for fine registration. Habboush et al[46] allowed interactive manipulation of images with real-time visual feedback to achieve accurate alignment between SPECT and MR brain data. Three types of fused 2D display were used, viz. color fusion and two forms of specific integration of features (masking and edge extraction). Hamilton et al[67] found that the autoregistration provided by the head-hat matching method[22] did not yield acceptable results for vascular registration of SPECT and CT images for the pelvic region. They, therefore, devised a completely manual tool for interactive registration by presenting fused displays of 3D wireframes and 2D color fusion images. Pfluger et al[68] compared automatic and interactive methods for MR-SPECT brain image registration and found that an interactive approach using 2D color fusion images had the lowest registration error. In addition, the influence of subjectivity was shown to be negligible.

Fused Display to Verify Registration Results

All methods discussed in the previous section on interactive registration were also used to verify registration results. In addition, others have applied fused displays to verify registration results where the emphasis is on methods for 2D integrated display. Adjacent display[13,20,37,44] and linked cursor/features[13,16,17,20] are the easiest forms. Some have used checkerboard displays,[13,16,34,49] but the usefulness appears limited to a research setting and presentation in articles. Evaluation of the registration accuracy in a clinical setting is much more critical, and the usefulness of the checkerboard is debatable as already mentioned earlier (see section on integrated 2D visualization). In the literature, the most prominently discussed—and therefore probably most useful—visualization techniques to assess registration accuracy are 2D color fusion[13,17,33,34,37,39,40,44,59,65,66] and 2D specific integration.[13,16,40,44,52,57,58]

Fused Display for Signal Enhancement

Combination of information from multiple sources can be applied to enhance conspicuity of relevant data with respect to irrelevant information. This area has been completely dominated by 2D color fusion methods for the assessment of multiparameter MR images or functional-anatomical data. The hybrid color MR imaging display of Weiss et al[26] combined corresponding MR T1 and T2 images into one single image based on the hue-luminance-saturation color model. They assigned the T1 data to the hue component and the T2 information to the luminance component of the corresponding pixel to enhance both data conspicuity and the efficiency of interpretation. Kamman et al[28] combined MRI T1 and T2 data into one directly interpretable image by uniquely mixing colors based on the RGB model. Although their monitor was limited to 8-bit color display, they found this color combination method a very suitable means of representation for the MR image data. Brown et al[29] integrated two or three parameter MR images into one image based on combination of RGB values whereby specific red, green, and blue color values were assigned to each of the MR parameters. They found that the increased tissue conspicuity potentially allowed the detection of subtleties that otherwise could have been missed by the observer. In addition, the limitations imposed by the 8-bit display caused information loss, but they considered this minimal. Alfano et al[37,43] described a method called "quantitative magnetic color imaging" (QMCI) to uniquely mix multiparameter MR images based on the RGB model. Whenever three MR parameter images had to be integrated each of the parameters was represented by using one of the RGB monochromatic scales. In the case when two MR parameter images had to be integrated a combination of monochromatic scales could be used as long as different pairs of MR parameters yielded two different composite colors. The authors found that QMCI maintained the diagnostic information from the original image data, with potential advantages in the assessment of brain abnormalities, such as tumors and white matter lesions. Several authors have applied 2D color fusion methods whenever the specificity of CT or MR by itself was not high enough to differentiate certain pathologies from normal variations. Color fusion of CT/MRI data with SPECT information for non-brain areas was used by a number of groups to increase specificity and thereby allowed improved differentiation of abnormalities.[31,35,65,66,67] Juengling et al[21] applied a method called SMART-PET for HSV color fused display of MRI T2 and PET data and found that signal hyperintensity in the MRI data correlated well with decreased PET accumulation in patients with white matter lesions.

Efficiency of Information Presentation to Facilitate and Improve Interpretation and Comprehension

Well chosen techniques for fused display are meant to increase the efficiency of information presentation and thereby to facilitate and to improve interpretation and comprehension of the data. Vera et al[59] qualitatively evaluated facility of interpretation for localizing seizure foci in subtraction SPECT and MRI data. Interpretation was found to be significantly higher when using overlay images compared with stand-alone analysis of ictal and interictal SPECT images (even when registered). Quarantelli et al[25] compared their frequency encoding (FE) method (summing the low frequencies of PET data with the high frequencies of MR T1 data) with two other techniques for fused (2D) display, viz. image averaging and color wash. Evaluators were asked to rate conspicuity of anatomical features from MR as well as PET abnormalities and PET activity distribution in images from seven patients and a computer-simulated phantom. The results suggested that evaluation of PET and MRI data can be improved by using FE. This diagnostic improvement has a considerable overlap with the previously mentioned items, most notably anatomical localization. Several associated diagnostic improvements can be distinguished:

Communication with Referring Specialists Improves

In our own work we found that the Normal Fusion images of SPECT difference data and MR images provided a summary of a large part of the data of epilepsy patients thereby not only facilitating the report of the results at the weekly neurosurgery meeting, but also linking the results with information from other sources, such as EEG, fMRI, and neuropsychiatric testing.[14,81,92]

Increased Confidence in Observations

Gandhe et al[55] obtained promising results when they tried to quantify the confidence of surgeons in their ability to interpret multimodal images. Stokking et al[89] asked nuclear medicine physicians to rate their confidence in localizing functional information with respect to the anatomy of the brain (see also the section on anatomical localization). 2D fused display based on adjacent display and linked characteristics increased the confidence of the observers compared with stand-alone SPECT display. 3D Normal Fusion images gave a further boost to their confidence in their ability to localize functional data.

Comparison Facilitated, Enhanced Intra- and Interobserver Reproducibility

The aforementioned study by Vera et al[59] found that the intra- and interobserver reproducibility was significantly higher when using fused display compared with stand-alone presentation. Stokking et al[92] found that Normal Fusion images of SPECT difference and MRI data made it easier to assess patterns of epilepsy related perfusion changes and thereby to facilitate the interpatient comparison.

DISCUSSION

Fused display of data from different sources is a powerful tool to retrieve relevant information contained within the original images. Evaluation of the different methods for fused display indicates that the diagnostic process improves, notably as concerns the anatomical localization (typically of functional processes), the registration procedure, the enhancement of signal, and the efficiency of information presentation (which increases speed of interpretation and comprehension). Consequently, fused display improves communication with referring specialists, increases confidence in the observations, and facilitates the intra- and intersubject comparison of a large part of the data from the different sources, thereby simplifying the extraction of additional, valuable information.

It is difficult to propose a standard method for fused display for a given diagnostic setting because the application of the visualization methods is not only task dependent (a diagnostic analysis typically involves several highly specific tasks and questions, each possibly demanding another visualization method), but also operator dependent. In most diagnostic settings the clinician is served best by providing several (interactive and flexible) 2D and 3D methods for fused display for a thorough assessment of the wealth of multiparameter and multimodal image information (see also Soltys et al[38]).

REFERENCES

1. Van den Elsen PA: Multimodality matching of brain images. Doctoral thesis, Utrecht University, the Netherlands, 1993

2. Levoy M: A hybrid ray tracer for rendering polygon and volume data. IEEE Comput Graph 10:33-40, 1990

3. Stokking R, Zuiderveld KJ, Hulshoff Pol HE, et al:. Integrated visualization of SPECT and MR images for frontal lobe damaged regions, in Robb RA (ed): Visualization in Biomedical Computing (Vol 2359). Bellingham WA: SPIE Press, 1994, pp 282-290

4. Evans AC, Marrett TS, Torrescorzo J, et al: MRI-PET correlation in three dimensions using a volume-of-interest (VOI) atlas. J Cerebr Blood F Met, 11:A69-A78, 1991(suppl 1)

5. Zubal IG, Spencer SS, Imam K, et al: Difference images calculated from ictal and interictal technetium-99mHMPAO SPECT scans of epilepsy. J Nucl Med 36:684-689, 1995

6. Levin DN, Hu X, Tan KK, et al: The brain: Integrated three-dimensional display of MR and PET images. Radiology 172:783-789, 1989

7. Viergever MA, van den Elsen PA, Stokking R: Integrated presentation of multimodal brain images. Brain Topogr 5:135-145, 1992

8. Britton K: Highlights of the annual meeting of the European Association of Nuclear Medicine, Lausanne 1994. Eur J Nucl Med, 21:159-169, 1994

9. Hawkes DJ, Hill DLG, Lehmann ED, et al: Preliminary work on the interpretation of SPECT images with the aid of registered MR images and an MR derived 3D neuroanatomical atlas, in Höhne KH, Fuchs H, Pizer S (eds): 3D Imaging in Medicine. Berlin, Springer-Verlag, 1990, pp 242-251

10. Hill DLG, Hawkes DJ, Crossman JE, et al: Registration of MR and CT images for skull base surgery using point-like anatomical features. Brit J Radiol 64:1030-1035, 1991

11. Holman BL, Zimmerman RE, Johnson KA, et al: Computer-assisted superimposition of magnetic resonance and high-resolution technetium-99mHMPAO and thallium-201 SPECT images of the brain. J Nucl Med 32:1478-1485, 1991

12. Drevets W, Videen T, MacLeod A, et al: PET images of blood flow changes during anxiety: Correction. Science 256: 1696, 1992

13. Hill DLG, Hawkes DJ, Hussain Z, et al: Accurate combination of CT and MR data of the head: validation and applications in surgical and therapy planning. Comput Med Imaging Graph 17:357-363, 1993

14. Chisin R, Pietrzyk U, Sichel J-Y, et al: Registration and display of multimodal images: Applications in the extracranial head and neck region. J Otolaryngol 22:214-219, 1993

15. Heiss W-D, Herholz K: Assessment of pathophysiology of stroke by positron emission tomography. Eur J Nucl Med, 21:455-465, 1994

16. Hemler P, Napel S, Sumanaweera TS, et al: Registration error quantification of a surface based multimodality image fusion system. Med Phys 22:1049-1056, 1995

17. Pietrzyk U, Herholz K, Schuster A, et al: Clinical applications of registration and fusion of multimodality brain images from PET, SPECT, CT, and MRI. Eur J Radiol 21:174-182, 1996

18. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al: FDG-PET scan in potentially operable non-small cell lung cancer: Do anatometabolic PET-CT fusion images improve the localisation of regional lymph node metastases? Eur J Nucl Med 25:1495-1501, 1998

19. Beyer T, Townsend DW, Brun T, et al: A combined PET/CT scanner for clinical oncology. J Nucl Med 41:1369-1379, 2000

20. Barnden L, Kwiatek R, Lau Y, et al: Validation of fully automatic brain SPET to MR co-registration. Eur J Nucl Med 27:147-154, 2000

21. Juengling FD, Kassubek J, Högerle S, et al: SMART-PET: Multimodality white matter imaging and display without loss of quantitative information. J Magn Reson Imaging 15: 456-461, 2002

22. Pelizzari CA, Chen GTY, Spelbring DR, et al: Accurate three-dimensional registration of CT, PET, and/or MR images of the brain. J Comput Assist Tomo 13:20-26, 1989

23. Viergever MA, Maintz JBA, Stokking R: Integration of functional and anatomical brain images. Biophys Chem 68:207-219, 1997

24. Rehm K, Strother SC, Anderson JR, et al: Display of merged multimodality brain images using interleaved pixels with independent color scales. J Nucl Med 35:1815-1821, 1994

25. Quarantelli M, Alfano B, Larobina M, et al: Frequency encoding for simultaneous display of multimodality images. J Nucl Med 40:442-447, 1999

26. Weiss KL, Stiving SO, Herderick EE, et al: Hybrid color MR imaging display. Am J Roentgenol 149:825-829, 1987

27. Levin DN, Pelizzari CA, Chen GTY, et al: Retrospective geometric correlation of MR, CT, and PET images. Radiology 169:817-823, 1988

28. Kamman RL, Stomp GP, Berendsen HJC: Unified multiple-feature color display for MR images. Magn Reson Med 9:240-253, 1989

29. Brown HK, Hazelton TR, Silbiger ML: Generation of color composites for enhanced tissue differentiation in Magnetic Resonance Imaging of the brain. Am J Anat 192:23-34, 1991

30. Lang TF, Hasegawa BH, Liew SC, et al: Description of a prototype emission-transmission Computer Tomography imaging system. J Nucl Med 33:1881-1887, 1992

31. Ricard M, Tenenbaum F, Schlumberger M, et al: Intraoperative detection of pheochromocytoma with iodine-125 labelled meta-iodobenzylguanidine: A feasibility study. Eur J Nucl Med 20:426-430, 1993

32. Sgouros G, Chiu S, Pentlow KS, et al:. Three-dimensional dosimetry for radioimmunotherapy treatment planning. J Nucl Med 34:1595-1601, 1993

33. Wahl RL, Quint LE, Cieslak RD, et al: "Anatometabolic" tumor imaging: Fusion of FDG PET with CT or MRI to localize foci of increased activity. J Nucl Med 34:1190-1197, 1993

34. Van Herk M, Kooy HM: Automatic three-dimensional correlation of CT-CT, CT-MRI, and CT-SPECT using chamfer matching. Med Phys 7:1163-1178, 1994

35. Scott AM, Macapinlac HA, Divgi CR, et al: Clinical validation of SPECT and CT/MRI image registration in radiolabeled monoclonal antibody studies of colorectal carcinoma. J Nucl Med 35:1976-1984, 1994

36. Tjuvajev JG, Macapinlac HA, Daghighian F, et al: Imaging of brain tumor proliferative activity with iodine131-iododeoxyuridine. J Nucl Med 35:1407-1417, 1994

37. Alfano B, Brunetti A, Arpaia M, et al: Multiparametric display of spin-echo data from MR studies of brain. J Magn Reson Imaging 5:217-225, 1995

38. Soltys M, Beard DV, Carrasco V, et al: FUSION: A tool for registration and visualization of multiple modality 3D medical data, in Loew MH (ed): Medical Imaging: Image Processing (vol 2434). Bellingham, WA, SPIE Press 1995, pp 74-80

39. Wong JC, Studholme C, Hawkes DJ, et al: Evaluation of the limits of visual detection of image misregistration in a brain fluorine-18 fluorodeoxyglucose PET-MRI study. Eur J Nucl Med 24:642-650, 1997

40. Hawkes DJ: Algorithms for radiological image registration and their clinical application. J Anat 193:347-361, 1998

41. Patton JA, Delbeke D, Sandler MP: Image fusion using an integrated, dualhead coincidence camera with X-ray tube-based attenuation maps. J Nucl Med 41:1364-1368, 2000

42. Callen DJ, Black SE, Caldwell CB: Limbic system perfusion in Alzheimer's disease measured by MRI-coregistered HMPAO SPECT. Eur J Nucl Med 29:899-906, 2002

43. Alfano B, Brunetti A, Ciarmiello A, et al: Simultaneous display of multiple MR parameters with quantitative magnetic color imaging. J Comput Assist Tomo 16:634-640, 1992

44. Chen C-T, Pelizzari CA, Chen GTY, et al: Image analysis of PET data with the aid of CT and MR images, in de Graaf CN, Viergever MA (eds): Information Processing in Medical Imaging. Planum Press: 1987, pp 601-611

45. Stokking R, Zuiderveld KJ, Viergever MA: Integrated volume visualization of functional image data and anatomical surfaces using Normal Fusion. Hum Brain Map 12:203-218, 2001

46. Habboush IH, Mitchell KD, Mulkern RV, et al: Registration and alignment of three-dimensional images: An interactive visual approach. Radiology 199:573-578, 1996

47. Zifko GA, Slomka PJ, Young GB, et al: Brain mapping of median nerve somatosensory evoked potentials with combined 99mTcECD single-photon emission tomography and magnetic resonance imaging. Eur J Nucl Med 23:579-582, 1996

48. Roolker W, van Buul MT, Broekhuizen A, et al: Improved wrist fracture localization with digital overlay of bone scintigrams and radiographs. J Nucl Med 38:1600-1603, 1997

49. Skalski J, Wahl RL, Meyer CR: Comparison of mutual information based warping accuracy for fusing body CT and PET by 2 methods: CT mapped onto PET emission scan versus CT mapped onto PET transmission scan. J Nucl Med 43:1184-1187, 2002

50. Zhang J, Levesque MF, Wilson CL, et al: Multimodality imaging of brain structures for stereotactic surgery. Radiology 175:435-441, 1990

51. Kapouleas I, Alavi A, Alves WM, et al: Registration of three-dimensional MR and PET images of the human brain without markers. Radiology 181:731-739, 1991

52. Maguire GQ, Noz M, Rusinek H, et al: Graphics applied to medical image registration. IEEE Comp Graph Appl 11:20-28, 1991

53. Evans AC: Correlative imaging, in Wagner HJ, Szabo Z, Buchanan JW (eds): Principles of Nuclear Medicine. Philadelphia, WB Saunders Co, 1995, pp 405-421

54. Matsuda H, Tsuji S, Shuke N, et al: Noninvasive measurements of regional cerebral blood flow using technetium-99m hexamethylprophylene amine oxime. Eur J Nucl Med 20:391-401, 1993

55. Gandhe AJ, Hill DL, Studholme C, et al: Combined and three-dimensional rendered multimodal data for planning cranial base surgery: A prospective evaluation. Neurosurgery 35:463-471, 1994

56. Koral KF, Zasadny KR, Kessler ML, et al: CT-SPECT fusion plus conjugate views for determining dosimetry in iodine-131-monoclonal antibody therapy of lymphoma patients. J Nucl Med 35:1714-1720, 1994

57. Mangin J-F, Frouin V, Bloch I, et al: Fast nonsupervised 3D registration of PET and MR images of the brain. J Cerebr Blood F Met 14:749-762, 1994

58. Andersson JLR, Thurfjell LA: Multivariate approach to registration of dissimilar tomographic images. Eur J Nucl Med 26:718-733, 1999

59. Vera P, Kaminska A, Cieuta C, et al: Use of subtraction ictal SPECT coregistered to MRI for optimizing the localization of seizure foci in children. J Nucl Med 40:786-792, 1999

60. Jannin P, Fleig O, Seigneuret E, et al: A data fusion environment for multimodal and multi-informational neuronavigation. Comp Aided Surg 5:1-10, 2000

61. Lewis PJ, Siegel A, Siegel AM, et al: Does performing image registration and subtraction in ictal brain SPECT help localize neocortical seizures. J Nucl Med 41:1619-1626, 2000

62. Graham MM, Muzi M, Spence AM, et al: The FDG lumped constant in normal human brain. J Nucl Med 43:1157-1166, 2002

63. Lee DS, Lee SK, Kim YK, et al: The usefulness of repeated ictal SPET for the localization of epileptogenic zones in intractable epilepsy. Eur J Nucl Med 29:607-614, 2002

64. Faber TL, McColl RW, Opperman RM, et al: Spatial and temporal registration of cardiac SPECT and MR images: Methods and evaluation. Radiology 179:857-861, 1991

65. Liehn J-C, Loboguerrero A, Pérault C, et al: Superimposition of computed tomography and single photon emission tomography immunoscintigraphic images in the pelvis: Validation in patients with colorectal or ovarian carcinoma recurrence. Eur J Nucl Med 19:186-194, 1992

66. Pérault C, Schvartz C, Wampach H, et al: Thoracic and abdominal SPECT-CT image fusion without external markers in endocrine carcinomas. J Nucl Med 38:1234-1242, 1997

67. Hamilton RJ, Blend MJ, Pelizzari CA, et al: Using vascular structure for CT-SPECT registration in the pelvis. J Nucl Med 40:347-351, 1999

68. Pfluger T, Vollmar C, Wismüler A, et al: Quantitative comparison of automatic and interactive methods for MRI-SPECT image registration of the brain based on 3- dimensional calculation of error. J Nucl Med 41:1823-1829, 2000

69. Hu X, Tan KK, Levin DN, et al: A volume rendering technique for integrated three-dimensional display of MR and PET data, in Höhne KH, Fuchs H, Pizer SM, (eds): 3D Imaging in Medicine. Berlin, Springer-Verlag, 1990, pp 379-397

70. Wallis JW: Three-dimensional display in SPECT imaging: Principles and applications, in Reiber JHC, van der Wall EE (eds): Cardiovascular Nuclear Medicine and MRI, 89-100. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1992, pp 89-100

71. Stimac GK, Sundsten JW, Prothero JS, et al: Three dimensional contour surfacing of the skull, face, and brain from CT and MR images and from anatomic sections. Am J Roentgenol 151:807-810, 1988

72. Wowra B, Schad L, Schlegel W, et al: Scopes of computer application in stereotactic neurosurgery, in Lemke

HU, Rhodes M, Jaffe C, et al (eds): Computer Assisted Radiology. Berlin, Springer-Verlag, 1989, pp 296-301

73. Ehricke H-H, Laub G: Combined 3D-display of cerebral vasculature and neuroanatomic structures in MRI, in Höhne KH, Fuchs H, Pizer SM, (eds): 3D Imaging in Medicine. Berlin, Springer-Verlag, 1990, pp 229-239

74. Evans AC, Collins DL, Neelin P, et al: Computer-integrated surgery, in Taylor RH, Lavallée S, Burdea GC, et al (eds): Correlative Analysis of Three-Dimensional Brain Images. Cambridge, MIT Press, 1996, pp 99-114

75. Parsai EI, Ayyanger KM, Dobelbower RR, et al: Clinical fusion of three-dimensional images using Bremsstrahlung SPECT and CT. J Nucl Med 38:319-324, 1997

76. Gering DT, Nabavi A, Kikinis R, et al: An integrated visualization system for surgical planning and guidance using image fusion and an open MR. J Magn Reson Imaging 13:967-975, 2001

77. Van den Elsen PA, Viergever MA, van Huffelen AC, et al: Accurate matching of electromagnetic dipole data with CT and MR images. Brain Topogr 3:425-432, 1991

78. Schiers C, Tiede U, Höhne KH: Interactive 3D registration of image volumes from different sources, in Lemke HU, Rhodes M, Jaffe C, et al (eds): Computer Assisted Radiology. Berlin, Springer-Verlag, 1989, pp 666-670

79. Payne BA, Toga AW: Surface mapping brain function on 3D models. IEEE Comput Graph 10:33-41, 1990

80. Valentino DJ, Mazziotta JC, Huang H: Volume rendering of multimodal images: Application to MRI and PET imaging of the human brain. IEEE T Med Imaging 10:554-562, 1991

81. Stokking R, Zuiderveld KJ, Hulshoff Pol HE, et al: Normal Fusion for three-dimensional integrated visualization of SPECT and magnetic resonance brain images. J Nucl Med 38:624-629, 1997

82. von Stockhausen H-M: 3D-visualisierung der Funktion und der Morphologie des menslichen Gehirns aus tomographischen Daten. Doctoral thesis, University of Cologne, Germany, 1998

83. Avery RA, Spencer SS, Studholme CS, et al: Reproducibility of serial peri-ictal single-photon emission tomography difference images in epilepsy patients undergoing surgical resection. Eur J Nucl Med 27:50-55, 2000

84. Stokking R, Studholme CS, Spencer SS, et al: Epilepsy related perfusion changes in the peripheral cortex. J Nucl Med 41:65P-66P, 2000 (abstr)

85. Zubal IG, Avery RA, Stokking R, et al: Ratio-images calculated from interictal positron emission tomography and single-photon emission computed tomography for quantification of the uncoupling of brain metabolism and perfusion in epilepsy. Epilepsia 41:1560-1566, 2000

86. Muzik O, da Silva EA, Juhasz C, et al: Intracranial EEG versus flumazenil and glucose PET in children with extratemporal lobe epilepsy. Neurology 54:171-178, 2000

87. Holländer I: Mapping the brain cortex using an analytical model of the head, in Yongmin K (ed): Medical Imaging: Image display. Proc SPIE 2431:478-489, 1995

88. Stokking R: Integrated visualization of functional and anatomical brain images. Doctoral thesis, Utrecht University, the Netherlands, 1998

89. Stokking R, van Isselt JW, van Rijk PP, et al: Integrated visualization of functional and anatomic brain data: A validation study. J Nucl Med 40:311-316, 1999

90. Pietrzyk U, Herholz K, Heiss W-D: Three-dimensional alignment of functional and morphological tomograms. J Comput Assist Tomogr 14:51-59, 1990

91. Pietrzyk U, Herholz K, Fink G, et al: An interactive technique for three-dimensional image registration: Validation for PET, SPECT, MRI and CT brain studies. J Nucl Med 35:2011-2018, 1994

92. Stokking R, Zubal IG, Viergever MA: Integrated visualization of functional and anatomical brain images. Physica Medica 17:259-265, 2001