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Review Article

Novel Quantitative Approach in Functional and Structural Imaging of Brain in Normal Aging and Neurodegenerative Disorders: Part I. Basic Considerations in PET and MRI

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Abstract

The advent of new neuroimaging modalities in recent decades, along with the increasing prevalence of neurological disorders and a rise in life expectancy over the past century, have collectively led to the numerous studies trying to explain the anatomical and functional changes in the human brain following the disease. Other investigators have attempted to find the differences in brain structures and functions following normal aging, since understanding age-related changes in the brain might be the first step to shed light on the pathophysiology of various neurological disorders. In this review, we describe the existing and novel quantitative approaches of functional positron emission tomography (PET) imaging. Moreover, we describe novel volumetric studies assessing global and regional volume changes based on advanced computerised techniques of magnetic resonance (MR) analysis such as voxel-based morphometry (VBM) and non-conventional MR techniques such as diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) followed by a brief review of arterial spin labeling (ASL) imaging.

Keywords: *Functional Neuroimaging; Brain; Neurodegenerative Disorders; Positron Emission Tomography; Magnetic Resonance Imaging*

Positron Emission Tomography Analysis

The PET analysis methods can be categorised into three main groups, as follows;

a) Qualitative Analysis

Visual assessment plays a vital role in the interpretation of PET studies in daily clinical practice. The interpretation relies on the comparison between metabolic activity in areas of interest and the adjoining background. This sort of assessment is especially appropriate to FDG-PET in recognising local glycolysis. Despite its simplicity, there may be inter- and intra-observer differences in PET interpretation due to the personal or subjective nature of visual assessment and the consequent lack of reproducibility, which becomes a cause of concern in diagnostic and therapeutic judgments and treatment monitoring where independent and neutral quantitative evaluation is needed.

b) Quantitative Analysis

Compartmental analysis models are a group of dynamic replicas that are used to evaluate the kinetics of materials quantitatively in physiological systems [1]. The constituents are the radiotracers or drugs and the kinetics processes to be measured can be the absorption, diffusion, transport and metabolism of substances such as glucose. Different compartment models can be used for quantitative PET analysis, for example, three tissue (four-compartment) compartment model, single tissue compartment model and two tissue (three-compartment) compartment model. Four-compartment model has six parameters, and the statistical properties of the model may not estimate all parameters at once. Single tissue compartment model is a simple model and is mostly applied to measure blood flow by ^{15}O labelled

water. Three-compartment model fits well with many tracers and typically is used for ^{18}F FDG. The three-compartment model generates a quantitative rate of metabolism that can assess FDG metabolism and yield distinct rate coefficients, therefore providing insight into the several aspects of glucose metabolism, such as phosphorylation and transport [2,3]. These three compartments mark off the FDG in plasma, and FDG as well as FDG-6-phosphate in the cell. Compartment 1 (C_1) represents the concentration of free plasma FDG in the arteries. The input function of this compartment cannot be calculated and requires measurements made by blood sampling. The first tissue compartment (C_2) characterises an extravascular accumulation of FDG in the tissue that is accessible for phosphorylation. Lastly, the compartment (C_3) is the FDG concentration that has been phosphorylated by hexokinase. K_1 and k_2 are the rate constants of onward and converse FDG transport, respectively. K_3 are the rate constant of FDG phosphorylation by hexokinase and K_4 are the rate constant of dephosphorylation by glucose-6-phosphatase. From a mathematical view, a compartmental model is a group of differential equations that describe the variation of mass in each compartment. The basic assumption of the equations is the mass balance in each compartment. The equations can be solved analytically and through optimisation. The intricacy of the expressions rises with the number of compartments. The solutions are non-linear when solving for the rate constants.

Dynamic scanning data with a quick sampling of arterial blood yield tissue-specific time-activity curves. These curves may be fitted using nonlinear minimum approximations of squares to retrieve the rate constants K_1-K_3. K_4 is too minor and is typically neglected, while kinetic modelling which comprises the dephosphorylation process can yield more precise results. The following equation is manipulated to determine the glucose metabolic rate (CMR_{glu}):

CMR_{glu}= Cp/LC * K1.K3/K2+K3

Where

C_p = plasma glucose concentration

K_1 = Clearance of FDG from blood to the tissue

K_2 = rate constant for clearance of FDG from tissue to the blood

K_3 = phosphorylation rate of FDG

LC = lumped constants relating FDG kinetics to that of glucose

Accurate determination of CMR_{glu} can lead to errors including the rate constants covariance, variance derived through the fitting process, partial volume effects, incorrect presumptions regarding the model and the influence of the activity of blood pool in the image data.

This quantitative approach has the advantages of having dynamic data available and less reliance on image time. However dynamic studies are complicated and require a lot of time and skill. They need a dynamic scanning procedure, which calls for arterial blood specimen selection to attain an input function.

Kinetic analyses described by Sokoloff et al. [4] and Schmidt [5] allow a reasonably accurate determination of cerebral MRglc (CMR_{glu}) from a single static scan too, however, determining the integrated supply of FDG to the tissue requires blood sampling of the arteries from injection time to the end of the scan. Hunter et al. [6] illustrated a simplified kinetic approach with a single time point that needs only a static scan and a single sample from veins through the scan to calibrate a population-derived average plasma curve. The question is how to approximate the zone under the blood time-activity curve without the need for measurements at multiple time points. Hunter discovered that, the input function in non-diabetic participants could be estimated by three decaying exponentials and that the two early exponents had a nominal difference. Therefore, any difference in the input function between patients was due to the late part of the curve. The amplitude of the third exponent was derived from a single late sample from the veins. Hence, the integral is approximated by a mixture of a tri-exponential function and a late sample from the veins. This approximated integral is then manipulated to return the FDG uptake to normal [7]. This technique has the disadvantage that the correction for differences in plasma clearance is merely a first-order correction.

Phelps et al. [2] and Huang et al. [8] established a 3-compartment model incorporating FDG-6-PO4 dephosphorylation to FDG for measurement of kinetic constants and local cerebral metabolic rate of glucose ($LCMR_{glc}$). These methods required dynamic PET data and multiple blood sampling. The result of LCMRGlc was reproducible. Venous blood sampling can be used instead of arterial blood sampling.

Multiple-time graphical analysis technique (Patlak-Gjedde graphic analysis) can be used in place of specific compartmental models, which was first illustrated by Patlak et al. [9] and Gjedde et al. [10]. The following equation is used to derive the local concentration at time t after injection:

$$C(t) = \lambda Cp(t) + Ki \int_0^t Cp(\tau)\, d\tau$$

Where

C(t) = tissue activity as measured by the PET scanner at time t

$C_p(t)$ = FDG concentration in the plasma

λ = distribution volume of FDG

k_i = net rate of FDG influx into tissue

τ = dummy integration variable

On both sides of the equation, the division is divided by the plasma concentration $C_p(t)$ to produce linearization that allows k_i to be calculated as the slope of a simple plot. However, this plot can only be used in a period in which (1) the free FDG in plasma has equilibrated to the FDG in all interchangeable tissue pools in the area of interest (e.g., white and grey matter), and (2) when there is no loss of product. The advantages of this method include its simplified protocol of scanning, the lack of noise amplification and the probability of achieving parametric images. The disadvantages include the requirement for dynamic scanning and the unavailability of separate rate constants K_1 and K_3.

A spectral analysis technique proposed by Cunningham et al. [11] grounded on a broader linear compartmental system can be used in place of the fixed kinetic model. This method does not need the number of compartments to be deductively fixed because it evaluates the minimum number of compartments that are required to specify the kinetics. This also gives approximates of the rate constant of the tracer trapping in the tissue, and the decay constants as well as the amplitudes of the reversible

components. The steady state of the system is not a requirement. This technique can be applied to cerebral blood flow, glucose utilisation, and ligand binding.

c) Semi-quantitative analysis

Standardized uptake values (SUV) is the most commonly used semi-quantitative index in clinical PET centres as it is less demanding technically, requires simple calculations and does not require a dynamic scan or a blood sample [12]. It is a measurement of normalised radioactivity concentration on PET images. It is calculated by using the following equation;

$$SUV = \frac{\text{Tissue activity concentration (MBq / mL)}}{\text{Injected dose (MBq) / Body weight (g)}}$$

SUV is typically estimated using computerised procedures by software in commercial PET scanners. SUV correlates with the glucose metabolism rate calculated by kinetic modelling [12]. Despite its convenient measurement, SUV has some limitations, and it is crucial to reduce the effects of variables which can be controlled. There are many patient-related, and technical-related factors affecting the reliability of SUV. Body size and serum glucose level are some factors related to the patient in this regard. Fat tissue has typically far less metabolism than other tissues leading to the exaggeration of SUV in other tissues of bulky subjects with high lipid content. Other parameters for SUV normalisation including body surface area and lean body mass are considered to be superior to using body weight [12-14]. Hyperglycemic states affect SUV measurement significantly affect SUV measurement. High serum glucose level can reduce FDG uptake in the target tissues due to a competition between FDG and serum glucose. Also, hyperinsulinemia increases glycolysis in muscles and adipose tissue which contributes to a decrease in the SUV measurement in other tissues. The serum glucose level is thresholded to a maximum of 150- 200 mg/dl before FDG-PET imaging is applied in many PET centres.

SUV measurement is affected by many technical factors. The period of uptake before image acquisition can be a variation factor. Most malignant lesions continue to take up FDG beyond interval of 45-60 minutes and do not attain a plateau for several hours. Thus, SUV measurement amid study sessions ought to be compared at the same time after tracer injection. Attenuation correction method and reconstruction method with highly smooth reconstruction can lead to underestimated SUV measurement. Hence, the use of a protocol with a standard reconstruction and acquisition algorithms for comparison among sequential imagings should be performed.

Partial Volume Effect and Partial Volume Correction

Unfortunately, PET imaging has many physical degrading effects, one of them is partial volume effect (PVE). PVE is a complexity between the real radioactivity distribution and the 3D point spread function (PSF) of the imaging formation course [15]. There are two different processes that produce PVE. Blurring of the 3D image due to the limited spatial resolution is the first one. Due to the limitation in resolution design of the detectors and the reconstruction process, a fragment of a signal from a smaller source pours out which is seen beyond the source, and it appears larger and dimmer. This can be applied to objects with sizes smaller than 2-3 times the spatial resolution of the PET scanner as determined by the full-width at half-maximum (FWHM). Therefore, with typical 6 mm FWHM effective PET resolution, tracer concentration within structure less than 12 mm in size will be underestimated. The other phenomenon which causes PVE is image sampling., the tracer distribution in PET is represented on a voxel grid, and evidently, the borders of the voxels do not match the original borders of the tracer distribution. Thus most voxels consist of different types of tissues. This phenomenon is often called the tissue fraction effect. The signal intensity of each voxel is the summation of counts of the underlying tissues included in that voxel [16].

PVE can not be ignored in brain PET imaging. The high uptake region (GM) appears to have a lower uptake level when there is leakage of signal from a region with higher activity to one with low activity. And the low uptake region (WM) appears to have a higher uptake. Therefore, it is important to differentiate between changes in radioactivity distribution due to PVE from the true changes in tissue function [17]. PVE becomes more crucial while studying neurodegenerative diseases using PET ligand. Alzheimer's disease (AD) is characterised by progressive cerebral atrophy and ventricular expansion which leads to a reduced volume of brain structures, especially, the GM regions [18-20]. This loss of volume produces a more pronounced effect by PVE. Hence, some changes on the PET image in regions of atrophy may be somewhat attributed to PVE. The PVE can obscure disease patterns that may be of interest while studying biomarkers [21].

The ideas of partial volume correction (PVC) for calculated values in minor lesions and total metabolic activity for evaluation of stages of the illness are the most promising concepts and might subdue deficiencies that are linked to the SUV technique. The goal of PVC is to reverse the effect of the system PSF in PET image and thereby restore the true activity distribution. PVC is hypothetically probable if both the spatial resolution of the PET scanner and the distribution of tissue components within the functional images are recognised. Structural imaging techniques with high resolution including MRI offer the required anatomical evidence which, together with the facts of scanner resolution, can be manipulated to increase the precision of PET functional images for PVE and attain more precise maps of the tracer distribution in various brain tissues and other tissues as well [22].

There exist several strategies for PVE correction. A more broad review of current correction methods can be readily found elsewhere [23]. They can be broadly classified into two groups according to the following principles. (1) Post-reconstruction-based PVC methods such as iterative deconvolution, recovery coefficient method, geometric transfer matrix method and multi-resolution approach and (2) Reconstruction-based PVC methods that apply instant Bayesian method, resolution recovery and anatomical priors. Among these methods, there are some approaches that manipulate the lesion size as defined by structural imaging data (e.g. CT/MRI) to correct for PVE. There are different brain MR segmentation techniques, such as region growing, clustering, edge detection, classifiers, Markov random field models, deformable models, artificial neural networks, atlas-guided, and many other methods that were mentioned in the previous section [17, 24, 25]. The following studies are prior,

and well-known PVC approaches using anatomy-based PVC from which recent studies are derived.

Herscovitch et al. [26] and Chawluk et al. [27] proposed the anatomy-based PVC method applied a whole brain PET data correction for metabolically inactive ventricular and sulcal volumes (cerebrospinal fluid (CSF) - acronym) as measured on computed tomography (CT). Average parenchyma values were obtained by dividing total brain PET data by the intracranial CSF percentage. However, GM and WM were not assessed separately. Moreover, this method allows for global correction of PET data but cannot be applied on a regional basis. Slansky et al. [28] subsequently used this method to apply for region of interest (ROI) data, manipulating corresponding fractional CSF values resulting from co-registered segmented MRI. However, in this method, the hypothesis was a single hot structure surrounded by cold tissue takes up the tracer. In fact, the GM is enclosed by both metabolically inactive CSF and WM which uptake tracer four times lesser than GM. Thus, the corrected outcomes are determined by the sum of WM included in ROI [22].

Meltzer et al. [29] subsequently proposed a PET imaging reconstruction process called a virtual PET. This process is based on PET/MR images and a 2-compartment model for PVC. The brain parenchyma segmentation acquired by MRI was degraded to the PET 2- or 3- dimensional resolution and subsequently a computer-generated PET of pure parenchyma was derived. Through dividing the real PET image by the corresponding virtual PET, PVC from the CSF was implemented on a pixel-by-pixel basis. This approach is merely for the GM activity loss as a consequence of spill out onto non-GM tissues which are supposed to have trivial tracer uptake and overlooked that tracer distribution in the brain is heterogeneous. It does not correct for partial volume averaging between GM and WM.

The third anatomy-based approach was proposed by Muller-Gartner et al. [30] and subsequently applied by Labbe et al. [31] It was extended to a 3-compartment model and enhanced to consider the diverse contributions from WM, GM and CSF. This method corrects for both the loss of GM activity as a result of spill out onto non-GM tissues and the gain in GM activity as a result of a spill in from adjacent WM. By multiplying the segmented image of WM with a tracer concentration of WM measured in areas where PVE was insignificant (e.g., centrum semi-oval), a virtual PET for WM was generated following by degrading it to the resolution of PET scanner. The WM computer-generated or virtual PET was then subtracted from the real PET image. The result denoted a selective real PET of GM. Then, a GM virtual PET image was created as explained earlier. The real PET of GM was then divided by the GM virtual PET to obtain a corrected GM-PET image. It assumes a homogeneous tracer distribution in WM and GM and activity in CSF to be zero. This method is analytically correct when GM tracer uptake in brain parenchyma is homogeneous, which may not always be true.

Because of limitation of previously described approach [29], Meltzer et al. [32] subsequently proposed 4-compartment model by including subcortical amygdala compartment. They claimed the major advantage of this method over the previous methods which is the accurate correction of small subcortical structures and irregular objects such as small cortical volume of interest (VOI) that can be defined by MR.

A more common method to multi-compartment analysis was then offered by Rousset et al. [33] using a matrix geometry-dependent transfer coefficients that exemplified the true activity fractions exchanged between each pair of brain regions because of PVE. It is a region-based method called the Geometric Transfer Matrix (GTM) technique that requires MRI parcellated into a set of non-overlapping ROIs. This approach considered both the spill out and spill in influences between any probable pair combination of ROIs, so creating a transfer matrix, which, with the matching PET values, established equations system with a solution that provides true ROI values [22]. Although this method is presented to correct regional measurement, the authors claim that it could be used on a pixel-by-pixel basis, decreasing the ROIs size to that of a pixel.

Rousset et al. [22, 34] also proposed the modification to the Muller-Gartner PVC method [30]. Because the WM virtual PET used in Muller-Gartner's PVC method based upon the information about the true WM concentration, which may be more or less precise depending on the measurement setting, using GTM method [33] to calculate WM value may take advantage of matrix transfer coefficients.

Wavelet-based correction that uses a wavelet transform to perform multi-resolution analysis was proposed by Boussion et al. [35] and Le Pogam et al. [36]. It involves the incorporation of high-resolution CT or MRI information into the low-resolution PET image. When there is a correlation between the anatomical and the functional images, the regions will be PVE corrected. This method has been further modified to incorporate an atlas by Shidahara et al.[37] to segment the anatomy. The PET image and the corresponding anatomical image are decomposed into several resolution elements. Then, high-resolution components of the PET image are replaced, in part, with those of the anatomical image after appropriated scaling. The results suggest that the introduction of the atlas improved quantification.

Last anatomy-based PVC reviewed here is included in the reconstruction-based method which firstly proposed to suppress noise. Bowsher et al. [38] proposed a method for reconstructing emission data while also segmenting it for relaxation of smoothness constraint. This method, called anatomical priors, used a Bayesian approach where prior probabilities were modified depending on whether a particular segmentation of a region was within boundaries observed in the anatomical segmentation. Bataille et al. [39] applied an anatomic prior method on the brain that was blurred to correct for PVE. The technique was shown to perform similarly with GTM method.

The central bases of possible inaccuracy in PVC approaches grounded on the virtual PET include inaccuracies of segmentation, the lack of the assumption of homogeneity of tracer concentration within the ROI, MRI-PET misregistration, inaccurate assessment of the PET resolution, and sources of activity not taken to account in the model. Anyone of these factors can affect the ultimate outcomes by interfering at various steps of the process, possibly with opposite effects (i.e., resulting in under- or overestimation) that may cause unpredictable influences [22].

Magnetic Resonance Imaging

Evidence of structural brain changes on a temporal scale has been growing as a result of a variety of emerging knowledge on normal development, aging, drug abuse, psychiatric disorder, and chronic health problem. While MRI provides a measurement of atrophy as a marker of the disease state, overlooking of structural differences in the configuration of individual brains by visual analysis or VOI may have happened. Voxel-based morphometry (VBM) is a current method for comparing changes in GM between groups of subjects. This approach is not influenced by one specific structure and gives an even-handed and inclusive calculation of anatomical variances all over the brain [40].

Conventional MRI technique provides the information on a macrostructural level, which most likely represents end-stage change; however, the underlying microstructural modifications remain unknown. MR-based techniques including diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) can analyse microscopic structure, especially white matter lesions, that is beyond the spatial resolution of conventional MRI. Perfusion measurement using H^{15}_2O PET is often considered the gold standard for quantitative measurement of cerebral blood flow (CBF) in humans. However, this method is cumbersome and generally cannot be performed in conjunction with MRI experiments [41]. MRI methods that offer quantitative CBF measurement would be of great importance for clinical use and research. Arterial spin labelling perfusion MRI (ASL-MRI) using magnetically-labeled arterial blood water as a tracer has emerged as a noninvasive and reliable modality for measurement of regional CBF [42]. It is directly analogous to H^{15}_2O used in PET measurement.

Image Segmentation and Volumetric Study

The process of image segmentation is to label each voxel in a medical image data set to specify its type of tissue or structure. This label can be a hard or soft segmentation; it can encompass a binary segmentation or a function that also represents the uncertainty or membership of each voxel [25]. Grayscale digital medical imaging of a CT or MRI scan is used as the input of the segmentation procedure. The output comprises the labels that categorise the voxels of input grayscale. Segmentation aims to provide more information than that exists in the original images. Application of image segmentation includes visualisation, volumetric measurement, building anatomical atlases, researching shapes of anatomical structures and tracking anatomical change over time. Novel imaging methods of measuring global and regional brain volume use the process of image segmentation to assess quantitative parameters of the brain. Image segmentation includes two associated tasks: delineation and recognition. Recognition is a process through which the object's locations in an image is approximately defined and does not include the exact description of the region occupied by the object. Delineation is the process of determining the object's detailed spatial size and configuration including gradation [24]. Several techniques for image segmentation are reviewed elsewhere [25, 43-45]. Some methods for quantifying brain volume can be simply divided into manual, semi-automated and fully-automated segmentation depending on the amount of user interaction.

There are preprocessing steps that improve image segmentation. Two examples of image artefacts associated with MRI images are the intensity inhomogeneity [46], a smooth intensity variation due to the image acquisition process; and the intensity variation of the same type of tissue in different acquisitions [47]. The artefacts corrections can improve the segmentation step tremendously, although we will not explore these preprocessing techniques.

A. Manual segmentation

Manual segmentation is one of the earliest methods of segmenting ROI by a skilled expert. The prototype of manual methods has been the manual segmentation of limbic structures, for instance, hippocampus and amygdala. In the past, specialists were interested in 2D measurements such as brain width, bicaudate ratio, and lateral ventricle width, whereas more recently, 3D segmentation has been performed for assessing brain volume. Manual segmentation is time-consuming, labour intensive, and suffers from the lack of reproducibility due to inter- and intra-observer variability. In particular, manual segmentation cannot be efficiently and practically performed in a large number of scans, such as a clinical trial.

B. Semi-automated and fully-automated MR segmentation

Segmentation means to divide the image into patches or regions that have common characteristics such as intensity, texture, shape or function. The segmentation algorithms usually use information from the voxel as well as information from nearby regions. In this review, we classified image segmentation in 3 groups: purely image-based, appearance model-based and hybrid [48]. Briefly, the details of some methods are described below.

B1. Purely image-based methods

The purely image-based segmentation methods use the information contained in the image to perform the segmentation. There can be some parameter input or initialisation by the user. Examples of those methods include threshold method, region growing, level sets, active contours, fuzzy connectedness, graph cuts, watersheds, Markov random fields and clustering.

"**Thresholding method**" is an intensity-based method to segment an image into two classes: foreground and background. The object is defined by an intensity range or set of intensity ranges. The voxels of the image within the range are classified as foreground. The method is simple and computationally fast. It is ideal for homogeneous tissues that can be easily split based on the intensity. In that case, the threshold value can also be automatically chosen based on the distribution of the intensities [49]. The thresholding method is sensitive to artefact and noise in MRI and also does not include any spatial information.

"Active contours model" or **"snakes"** is an energy-minimising technique for delineating the region boundaries. The initial contour is actively deformed to find the desired boundary. In a closed contour, the energy functional to be minimised depends on internal energy that is intended to preserve the curve smoothness and an image energy term that guides the forces toward lines and edges. Active contour distorts to fit the shape

of the object by reducing a gradient-dependent attraction force while simultaneously preserving the softness of the contour that provides robustness to noise and spurious edges [50].

"**Markov random field models**" is a statistical model that can be used in segmentation. This method allows one to model the spatial interactions between neighbouring voxels. These correlations provide a mechanism for modelling a variety of image properties [25].

"**Clustering method**" is an unsupervised learning technique, where one needs to identify a finite set of categories, known as clusters, to classify voxels. Features based on the voxel or set of voxels, such as intensity, gradient, spatial information or texture, are the input elements. The clustering depends on a similarity function defined between the features. The similar features are then grouped into classes, and the corresponding similar voxels are clustered. The grouping can be based on a different criterion, for instance, the principle of maximising the intra- and minimising the inter-class similarity. Three common algorithms are the expectation-maximisation, k-means clustering and fuzzy c-means clustering [25,51].

"**Region growing method**" requires a seed point that is manually selected by an operator and extracts all pixels connected to the initial seed based on some predefined criteria. It is seldom used alone but usually within a set of image-processing operations, particularly for the delineation of small, simple structures.

B2. Appearance model-based methods

The appearance model-based methods use models that contain information about the object to be segmented. Examples of such methods include active shape models and atlas-based methods.

"Active shape models" is a deformable model-based technique. The models are a statistical representation of the shape variations from training sets. The shape is represented by a point distribution with mean position and principal modes of variation. This approach allowed flexibility to fit different shapes but constrained to what was observable in the training set [52].

"**Atlas-guided approaches**" are potent tools when a standard atlas or model is accessible. The atlas contains not only intensity information but also the shape/morphology of the region to be segmented. The atlas is generated by compiling information on the interested anatomy that required segmentation. The atlas is used as a reference space for segmenting new images. Images are mapped into the same space (e.g. Tailarach brain atlas and diffeomorphic metric mapping [53, 54]) and the structures can then be labelled and also compared. The problem with the atlas method is to define a precise and vigorous registration, particularly for complex structures. Thus it is better suited for structures that have less anatomical variability among the population of study.

B3. Hybrid

The hybrid method combines both purely image-based and appearance model-based methods.

"Oriented active shape models" combine properties of "active shape models" with the boundary orientation concept of live wire technique. This method effectively separates an object border from other non-object borders with similar features particularly when they get too close in the image field. This method results in a two-level programming technique that is dynamic and its first level represents boundary recognition and its second level corresponds to boundary delineation. This technique yields an optimal border that approves the shape model if the recognition phase is successful in bringing the model close to the boundary in the image. The precision of this method was suggested to be better than that of "active shape method" [55].

Brain volumetric studies based on manual or semi-automated ROI measurements may be inherently biased due to the small number of regions and metrics used in classical morphometrics that are insensitive to changes elsewhere in the brain [56]. There has been an emerging number of unbiased, automated whole brain techniques that can improve the resolution of structural MRI and image processing tools. One technique that is required to register images from large cohorts into a common stereotactic space and allows a voxel-wise comparison is named VBM [40].

Voxel-based Morphometry

VBM is an automatic method and is not biased to one certain structure and gives an even and inclusive valuation of structural differences in the brain [40]. Employing 3D volumetric T1-weighted image, VBM manipulates statistics to recognise variances in brain anatomy between groups of the subject, which in turn can be used to show the existence of atrophy or tissue expansion in diseased subjects. It compares local brain tissues between two groups of subjects and tests for residual tissue concentration differences that remain after all MRI scans are spatially normalised into the same standardised stereotactic space. By exploring the whole brain, VBM provides a measurement of highly localised regions that may not be seen by other techniques that use more labour intensive ROI measurement.

VBM processing begins with ***spatial normalisation*** which aims to match multiple MRI scans from different individuals thus a position in one subject's scan represents the same location in another subject's scan. This stage is attained by registration of all images from a study onto the same template image making them into the same space. Nonlinear transformation is typically included in this procedure. Templates that are produced using the study cohort or a cohort corresponding to the study in terms of age, the status of disease, scanner field power, and scanning factors are suggested for registrations that use a mean squared difference matching function to enhance the standardization between each subject on the study cohort and template [56]. Next step is ***segmentation*** where images are segmented into difference tissue compartments as GM, WM and CSF. The analysis is done independently on either GM or WM, depending on the question being enquired [57]. Due to nonlinear spatial standardisation based on separate cosine transforms in a common VBM package Statistical Parametric Mapping (SPM), the volumes of certain brain regions may grow, whereas others may shrink. A further process, called ***modulation***, is incorporated to maintain the volume of the specific tissue inside a voxel. Voxel values are multiplied by modulation in the segmented images by the Jacobian determinants resulting from the anatomical standardisation phase. In actuality, an analysis of modulated data tests for local variations in the absolute GM volume, whereas analysis of unmodulated data tests for regional differences in the concentration of GM [58]. If the spatial

standardisation was precise and all the segmented images seemed equal, no major dissimilarity would be identified in unmodulated data [57]. Finally, each optimally standardised, segmented, modulated image undergoes a ***smoothing*** process, whereby each voxel intensity is supplanted by the weighted average of the adjacent voxels. The voxels number averaged at each point is defined by the smoothing kernel size. The smoothing phase aids to compensate for the imprecise nature of the structural standardisation. Also, it renders data normally distributed, improving the validity of the parametric statistical test and decreases intersubject unevenness.

Statistical analysis of the segmented smoothed images is usually achieved with parametric statistics using the general linear model (GLM). GLM is used to identify regions of GM concentration that are significantly related to the particular effects under study. Standard parametric statistical procedures include the *t*-test and *F* tests, which are used to test the hypotheses. The significance of any difference is ascertained by the use of the theory of Gaussian random fields [59]. The null assumption is that there is no variance in tissue volume between two groups. VBM generates statistical maps presenting all voxels of the brain that refute the null and show substantial to a certain, user-selected, *p*-value [57].

Errors and variability in the analysis of VBM can be introduced. For instance, this technique cannot discriminate real variations in tissue volume from local misregistration of images [40]. The accuracy of normalisation and segmentation can vary across the brain regions. Partial volume effects, especially in the atrophic brain can make segmentation error.

There are several variabilities across VBM studies such as processing steps, a *p*-value of each statistical analysis and different corrections for multiple comparisons, the number of subjects in control and disease cohort, age, gender ratio, and disease severity across groups. Therefore, interpretation of data across VBM studies might be a problem because a comparison of *p* values or *t* statistic in studies is not significant, and only offers little evidence of a variation between diseases and various cohorts of the same disease. VBM technique can also be used to other imaging modalities such as functional MRI and PET. Because of the statistical nature of the technique, It should be reiterated that VBM provides essential information about regions through the group, but cannot offer reliable information for single-subject diagnosis [57].

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