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Guidelines for Developing Automated Quality Control Procedures for Brain Magnetic Resonance Images Acquired in Multi-Centre Clinical Trials

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1. Introduction

Automated quality control (QC) procedures are critical for *efficiently* obtaining *precise* quantitative brain imaging-based metrics of in vivo brain pathology. This is especially important for multi-centre clinical trials of therapeutics for neurological diseases, in which brain imaging-based metrics may be used to quantify therapeutic efficacy. While there are many different types of brain imaging methods (e.g. computed tomography, magnetic resonance imaging, positron emission tomography, etc.) that have been used to quantify different aspects of in vivo pathology (e.g. presence of tumours, brain atrophy, hydrocephalus, abnormalities in blood vessels or the extravasation of blood, the depletion of receptors available for the binding of an injected substance, abnormal brain metabolism, etc.), this Chapter will focus on the automated QC procedures required to use magnetic resonance (MR) images (MRI) to yield imaging-based metrics of in vivo brain tissue pathology.

Magnetic resonance imaging is a powerful non-invasive technology that can provide in vivo images sensitive to normal and pathological brain tissue. Important strengths of MR imaging include its superior grey-matter (GM)/ white-matter (WM) tissue contrast, sensitivity to WM pathology and clinical feasibility of relatively high-resolution whole-brain imaging. In conventional brain MRI, the signal intensities arise from the different relaxation characteristics of protons in water molecules present in different brain environments following radio-frequency (RF) excitation when the brain is in a magnetic field. MRI acquisition sequences vary the timing and duration of RF excitation pulses and magnetic field gradients, yielding different contrasts (termed MRI modalities) that can highlight different aspects of brain anatomy and pathology. This is illustrated in Fig. 1 using 4 conventional imaging modalities, T1-weighed (T1w) and T1w 5 min after intravenous injection of a gadolinium (Gd) contrast agent (T1w+Gd), T2-weighted (T2w), proton density weighted (PDw), and fluid attenuated inversion recovery (FLAIR) image, which were all acquired from a patient with multiple sclerosis (MS), a neurological disease that affects the brain and spinal cord. The T1w image most clearly differentiates brain GM, WM and

cerebrospinal fluid (CSF). This high tissue contrast is the reason why T1w is often the optimal input modality, or included with other input modalities, for image-processing algorithms that classify the image voxels (volume elements) as WM, GM and CSF, which can be a critical step that precedes the quantification of biologically important brain characteristics (e.g. the volumes of the entire brain, individual brain structures, GM, WM, and abnormal WM and GM). In addition to the high tissue contrast, T1w MRI also informs on brain pathology. It has been shown that WM hypointensities on T1w MRI of MS patients are associated histopathologically with severe tissue destruction (Van Walderveen et al., 1998), and T1w MRI also reveals a population of hypointense lesions in the cerebral cortex of MS patients (Bagnato et al., 2006). By injecting a Gd contrast agent (Gd is paramagnetic in its trivalent state), the T1w modality can be further exploited to detect increased permeability of the "blood-brain barrier" (BBB), which under normal conditions restricts the transport of substances from the circulation into the brain, thus confining the Gd contrast agent to the blood vessels and resulting in a relatively bright intensity of blood vessels large enough to be resolved by T1w imaging. Under pathological conditions (e.g. stroke, trauma, tumour, inflammation), the permeability of the BBB may be transiently increased and the Gd contrast agent will enter the brain, resulting in a relatively bright intensity in the region of the pathology. For example, in Fig. 1 the T1w+Gd image from a patient with MS exhibits a ring of hyperintense signal that results from the increased BBB permeability associated with acute focal inflammation. The T2w image is more sensitive to different types of WM pathology (not only the severe tissue destruction) than the T1w, exhibiting abnormally hyperintense signal in regions with pathological abnormalities such as: tissue loss, injury, incomplete repair, inflammation and scarring. Important limitations of using T2w images to quantifying brain pathology is the lack of specificity of the hyperintensities (e.g. they may be oedema that may resolve quickly, they may be irreversible tissue destruction that may never repair and result in further degeneration), and the poor CSF/ abnormal WM contrast (e.g. abnormal WM that abuts the CSF-filled ventricles cannot be reliably quantified). The latter limitation is addressed by acquiring PDw and FLAIR images, in which abnormal WM is hyperintense and CSF is hypointense. Furthermore FLAIR imaging has been shown to be more sensitive to focal WM MS pathology compared to standard T2w imaging (De Coene et al., 1992; Filippi et al., 1996; Geurts et al., 2005).

In clinical trials of therapies for neurological diseases (e.g. multiple sclerosis and Alzheimer's disease), various MRI modalities may be acquired within a single scanning session to quantify various aspects of brain pathology, and multiple scanning sessions may be performed on each patient throughout the trial to track the changes in MRI-derived brain pathology metrics from the baseline pre-treatment state (Fig. 2). This *multiple imaging modalities at multiple timepoints for many patients* paradigm to yield a snapshot of the brain pathology at a certain timepoint or to yield the dynamics of progressing/ resolving pathology, relies upon the assumption that image intensity variations are biological. Within this assumption, MRI-derived brain pathology metrics may be calculated using an image-processing pipeline comprised of leading edge automated techniques including image intensity normalization, co-registration of different MRI modalities, registration to brain atlases, brain tissue classification, segmentation of brain structures and types of pathology (Fig. 2 – Image Processing Pipeline). The success of these automated image-processing techniques may be significantly affected by spatial and/ or temporal variability in the MRI intensities resulting from methodological sources including scanner software/ hardware

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upgrades, scanner hardware deterioration and human error (Fig. 2 – MRI Acquisition). Accordingly, the role of QC is to ensure that each MRI that enters an image-processing pipeline has been assessed and meets an acceptable level of quality (minimally affected by non-biological variability, consistent with trial protocols, and consistent with previously obtained data from the patient during the trial) to ensure the expected accuracy and precision of the MRI-derived brain pathology metrics (Fig. 2 – Quality Control).
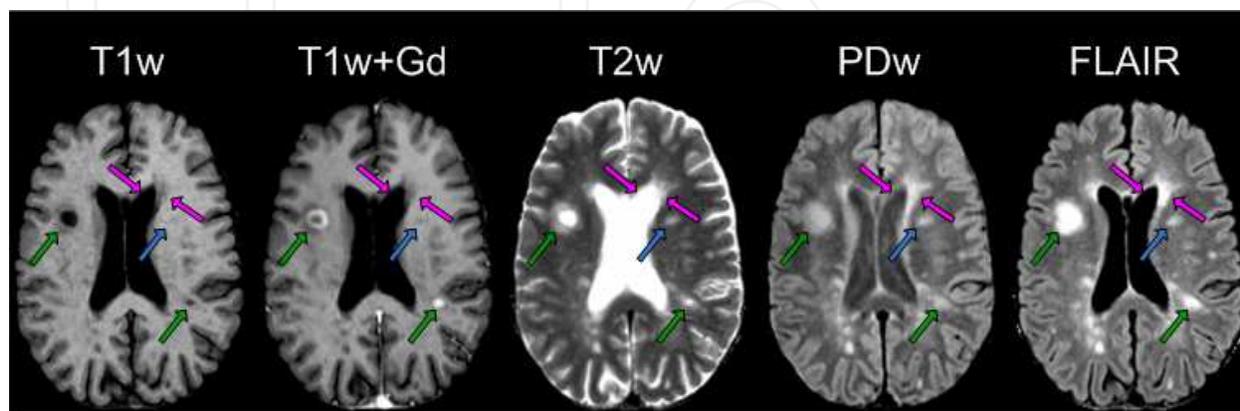

Fig. 1. Corresponding 2D slices extracted from different 3D MRI modalities acquired during a single scanning session of a patient with MS. (Left to right): T1-weighed (T1w), T1w after Gd injection (T1w+Gd), T2-weighted (T2w), proton density weighted (PDw) and fluid attenuated inversion recovery (FLAIR). Green, purple, and blue arrows highlight the advantages and disadvantages of each MR modality. Green arrows show acute increases in BBB permeability (hyperintense signal on T1w+Gd) associated with tissue destruction and inflammation (hypointense signal on T1w; hyperintense on T2w, PDw and FLAIR), and purple arrows show the weakness of T2w images in differentiating abnormal WM from adjacent CSF (better differentiation on PDw and FLAIR). Overall, the volume of abnormal WM on T2w and FLAIR modalities may be higher than on T1w, due to their high sensitivity to various pathological processes (e.g. swelling, destruction, repair, scarring)

This Chapter provides guidelines for developing an automated QC procedure for brain MRIs acquired in multi-centre clinical trials of therapeutics for neurological diseases; in particular the automated QC for multi-centre clinical trials of therapies for MS will be discussed in detail. Emphasis will be placed on: 1) demonstrating the need for appropriate QC procedures, 2) determining the objectives, 3) defining quality, 4) developing a framework to facilitate the creation of quality control procedures for MRIs, and 5) providing an example of an automated QC procedure that is used in industry. Although the focus will be on QC for clinical trials of MS therapies, the guidelines proposed in this chapter could be applied to clinical trials that use MRI-based imaging metrics to assess therapeutics for other neurological disorders such as Alzheimer's disease, epilepsy, sleep apnea, stroke, and amyotrophic lateral sclerosis.

2. Demonstrate the need for appropriate QC procedures

It may seem obvious that if an MRI scan is adequate for qualitative interpretation by a radiologist, then it should be of sufficient quality to be used to extract quantitative metrics of brain pathology, however, this is not necessarily true. Studies have been performed

demonstrating the effect of specific aspects of MRI quality on specific types of MRI-based imaging metrics.

Preboske et al. (2006) compared the effect of three types of common MRI artifacts, inconsistent image contrast between serial scans, head motion, and signal-to-noise ratio (SNR), on the performance of the boundary shift integral (BSI), a method used to quantify whole brain atrophy between MRIs acquired in the same person at two different visits, by calculating the shift at the brain tissue/ CSF border that may occur over the time between the visits if the brain is undergoing volume loss. They found that as image quality deteriorated due to any of the three types of artifacts, the atrophy measurement error increased. The study showed that the magnitude of error could substantially exceed the disease effect in Alzheimer's Dementia (AD) for whole brain atrophy per year (Preboske; Gunter; Ward & Jack, 2006). Blumenthal et al. (2002a) compared the effect of ringing artifacts caused by subject movement on measuring grey matter volume using ANIMAL (Kuba et al., 1999) in 180 healthy children. The authors compared the amount of ringing present (none, mild, moderate, or severe) in the MRI to the volume of brain classified as grey-matter and found that as the level of motion increased, the volume of grey matter decreased. Camara-Rey et al. (2006) examined the effect of simulated motion artifacts (ghosting, blurring, and pulsatile flow artifacts from major blood vessels like the carotid arteries) on measuring brain atrophy using SIENA (Smith et al., 2004; Smith et al., 2002). In healthy subjects they found that the presence of these artifacts could substantially affect atrophy measurements and, in some cases, have the same expected differences observed in AD patients over a 12 month period. Boyes et al. (2006) compared two methods for measuring brain atrophy measurements, the BSI and Jacobian integration (JI), using MRIs from a cohort of AD patients and healthy subjects. Three scans were acquired for each subject, a same day scan and repeat scan (re-scan) pair to determine the inherent error of each method and a scan one year later to assess the consistency of each method. Each scan was visually assessed for image quality by an experienced MRI reader based on motion artifacts and contrast differences between WM and GM, and brain and CSF. They showed that the BSI and JI techniques were susceptible to poor image quality with measurement errors exceeding three times the expected brain atrophy rate observed in normal control elderly subjects over 1 year (Scahill et al., 2003) and within the range of yearly atrophy rates observed in AD patients (Bradley et al., 2002; Fox et al., 2000).

These studies demonstrate the potential for the quality of an MRI to affect the quantification of brain metrics by adding variability that can obscure pathological changes. A QC procedure should objectively quantify the quality of an image and subsequently objectively reject images with quality metrics that do not meet software-specific a priori defined control limits.

Complexities of Developing QC procedures for Clinical Trials

While the QC studies discussed in the preceding paragraph(s) demonstrated the effect of some aspects of MRI quality on a subset of MRI-based brain metrics calculated in relatively few subjects, multi-centre clinical trials pose additional QC-related difficulties: 1) large volume of MR images acquired from multiple subjects at multiple timepoints, 2) scanner variability arising from variations in hardware performance, 3) hardware and software changes, 4) human error, 5) diversity of MRI-derived brain pathology metrics, and 6) variety of image processing methods involved in the measurement of these brain pathology metrics.

The sheer volume of MR scans that are produced by multi-centre clinical trials limits the feasibility of MRI readers to manually assess each MRI for image quality (De Stefano et al., 2010; O'Connor et al., 2009; Rovaris et al., 2008). With the human visual system and time as constraints, MRI readers cannot consistently evaluate MRI images for correct identification (Does the brain MRI actually correspond to the patient identifier?), correct MRI sequence (Do the scanning parameters match the protocol?), and acceptable image quality (Is the noise, motion, etc., within acceptable ranges of the control limits?).

Scanner variability arising from day-to-day variations in hardware performance and deliberate changes to the scanner hardware or software may result in variations in the MRI characteristics, which could introduce non-biological variability in MRI-derived pathology metrics. While a QC procedure may not be capable of detecting the most subtle variations in hardware performance (which may not significantly affect MRI-derived metrics), the QC procedure would be expected to detect failing and noted software changes.

The most common human errors in MRI acquisition in the clinical trial setting are: Mistyping of a patient identifier or using the incorrect patient identifier, acquiring MRI sequences with incorrect parameters or omitting MRI sequences, and acquiring MRI modalities in the wrong scan order (which can be critical, for example, when injection of a contrast agent is essential for a certain modality but may corrupt other modalities). An automated QC procedure can detect mistyped patient identifiers and detect incorrect patient identifiers by assessing if the present brain MRI is the same brain as other MRIs with the same identifier. Incorrect sequence parameters or missing sequences can be detected by an automated QC that compares the MRI sequences acquired in a session to the previously accepted protocol- and site-specific sequences and parameters. Incorrect acquisition order of MRI modalities can be detected by comparing the acquisition times of each scan to the previously accepted protocol- and site-specific scan order.

The diversity of the MRI-derived brain pathology metrics will also influence the QC procedure. Image quality may not be acceptable for some metrics, but may be adequate for others. For example, a localized image artifact that prevents the volume of a specific small brain structure such as the hippocampus from being measured reliably may not significantly affect the measurement of total brain white matter tissue volume. The ideal QC procedure should have the flexibility to detect and report image quality issues that prevent the reliable calculation of a specific metric, without rejecting the entire scanning session as a whole.

The variety of image processing methods to measure brain pathology metrics is another factor that can impact the QC procedure. Image quality may affect some image processing methods more than others. For example, a single-modality K-means classifier will be affected by poor SNR or ghosting more than multi-modal classifiers because they do not have complementary data. The automated QC procedure should account for the limitations of image processing tools used to calculate brain pathology metrics.

The impact that MRI quality can have on MRI-derived brain pathology metrics combined with the difficulties associated with multi-centre clinical trials demonstrates the need for appropriate QC procedures.

3. Process pipeline for multi-centre clinical trials

It is helpful to understand the intricacies of multi-centre clinical trial MRI process pipelines before proceeding to the guidelines section for developing quality control procedures for
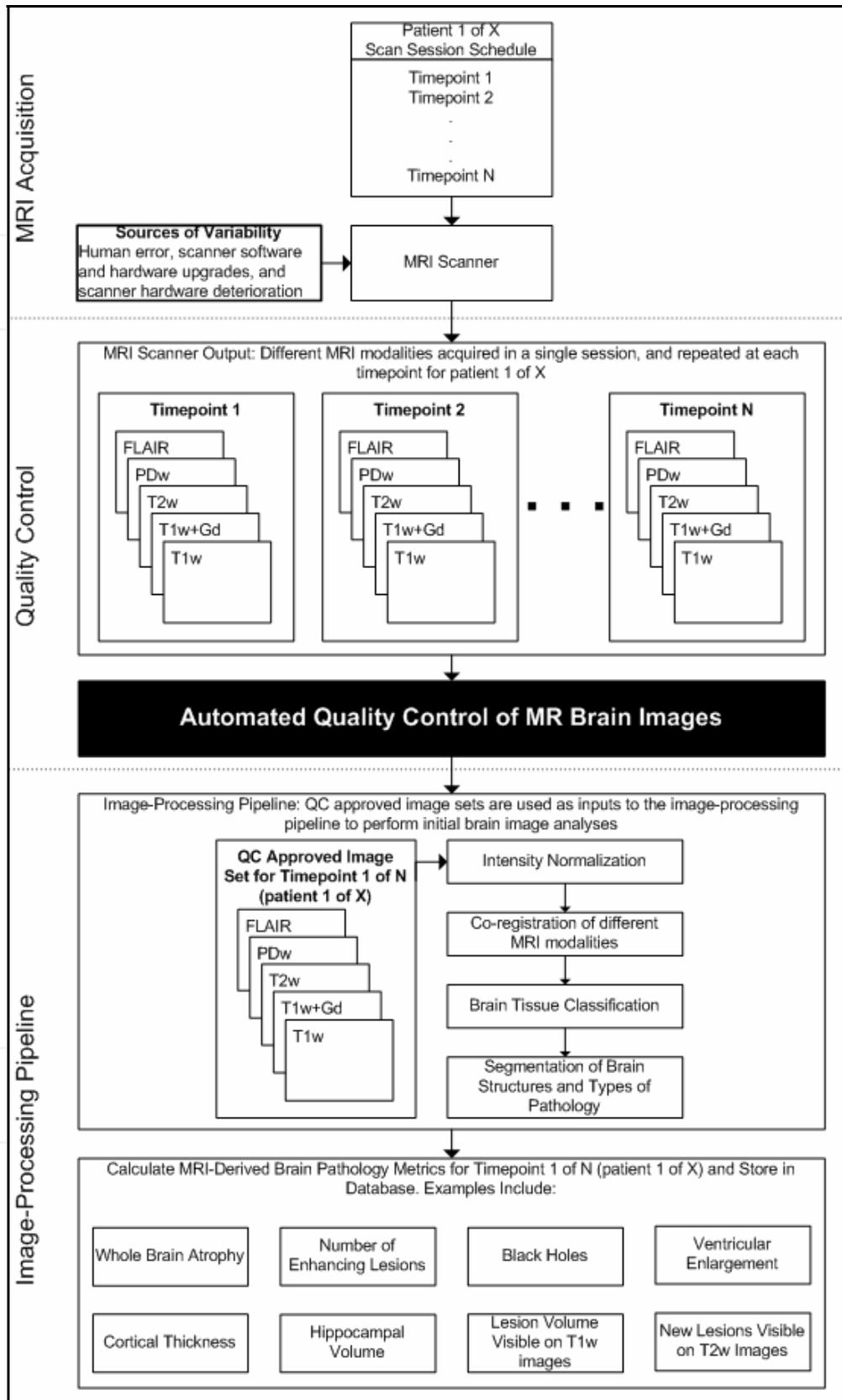
Fig. 2. An example of an MRI process pipeline for a multi-centre clinical trial. The pipeline consists of: 1) MRI Acquisition, 2) Quality Control, and 3) Image-Processing Pipeline

brain MRIs. Fig. 2 illustrates three components common to most process pipelines for multi-centre clinical trials, 1) acquisition of MRIs, 2) quality control of MRIs, 3) and image-processing of MRIs and quantification of the MRI-derived brain pathology metrics.

Acquiring multi-modal MRIs (e.g. FLAIR, PDw, T2w, T1w, T1w+Gd) from multiple subjects across multiple timepoints at various scanning sites forms the initial step of the pipeline (Fig. 2 – MRI Acquisition). Unfortunately, as discussed in Section 2, these images may be affected by human errors as well as non-biological variability introduced by the scanner. Without the quality control step (the second step in Fig. 2) these errors and non-biological variability would be propagated down the MRI process pipeline, thereby affecting the fidelity of MRI-derived brain metrics. Accordingly, quality control procedures are placed early in the MRI process pipeline, in which the image sets are submitted to a set of QC tests. Unacceptable images are flagged by comparing the QC test results to pre-determined control limits, logged in a QC database, prevented from further processing, and reviewed by imaging experts to identify the root cause of the error, while acceptable MRI sets are normalized to correct for intensity non-uniformities when appropriate, co-registered and processed using brain tissue classifiers and segmentation techniques to identify brain tissues and regions of interest (Fig. 2 – Image-Processing Pipeline). The resultant images and their corresponding maps of tissue type and locations of critical brain structures may then be used to calculate brain pathology metrics such as: total brain volume loss; increases in the CSF-filled lateral ventricles; cerebral cortical thickness; the volumes of specified brain structures; the number of white-matter lesions that are new, contrast-enhancing or associated with tissue destruction. These metrics are but a few examples of MRI-derived metrics which may be used to quantify disease evolution or therapeutic efficacy.

4. Guidelines

This section provides a set of guidelines for developing an automated QC procedure for brain MRIs acquired in multi-centre clinical trials of therapeutics for neurological diseases with a focus on multiple sclerosis. The sub-sections include defining quality and developing quality control procedures for brain MRIs.

4.1 Quality

The American Society for Quality (ASQ) states that in technical usage, quality can have two meanings: 1) the characteristics of a product or service (e.g. MRIs) that bear on its ability to satisfy stated or implied needs (e.g. accurate and reliable brain pathology measurements) and 2) a product or service free of deficiencies (ASQ, n.d.). In engineering usage, G. Taguchi provides a similar definition of quality as having two types: 1) customer quality (features what customers want, i.e. multi-center clinical trial sponsors would like MRIs that provide accurate and reliable brain pathology measurements) and 2) engineered quality (problems customer does not want) (Taguchi et al., 2000). Princeton's wordnet defines quality as the degree or grade of excellence or worth (Princeton, 2010).

In the case of multi-centre clinical trials of therapeutics for neurological diseases where therapeutic efficacy is evaluated using brain pathology metrics derived from MRIs, the definition of quality should be based on the value an MRI has towards its intended application. Accordingly, quality can be defined as the degree of worth of an MRI to measuring brain pathology metrics which is in accordance with the ASQ's and G. Taguchi's definitions of quality.

4.2 Developing QC procedures for brain MRIs

In accordance with the above definition of quality, the following sub-sections detail a framework that can be used to develop QC procedures for brain MRIs acquired in multi-centre clinical trials for neurological disease. Sub-sections include 1) factors that impact quality, 2) determining important QC tests, 3) imaging markers for QC tests, 4) determining the degree of worth of MRIs, 5) creating control limits to assess (pass and fail) MRIs, and 6) determining a course of action to take: accept, correct, or reject the MRI

Factors that Impact Quality

Non-pathological and non-physiological anomalies present on MRIs (image artifacts) and scan-to-scan variations in trial-, site-, and subject- specific acquisition protocols and sequences (longitudinal inconsistencies) are two important factors that can affect image quality. Image artifacts may result from subject movement, defective hardware, Gibb's
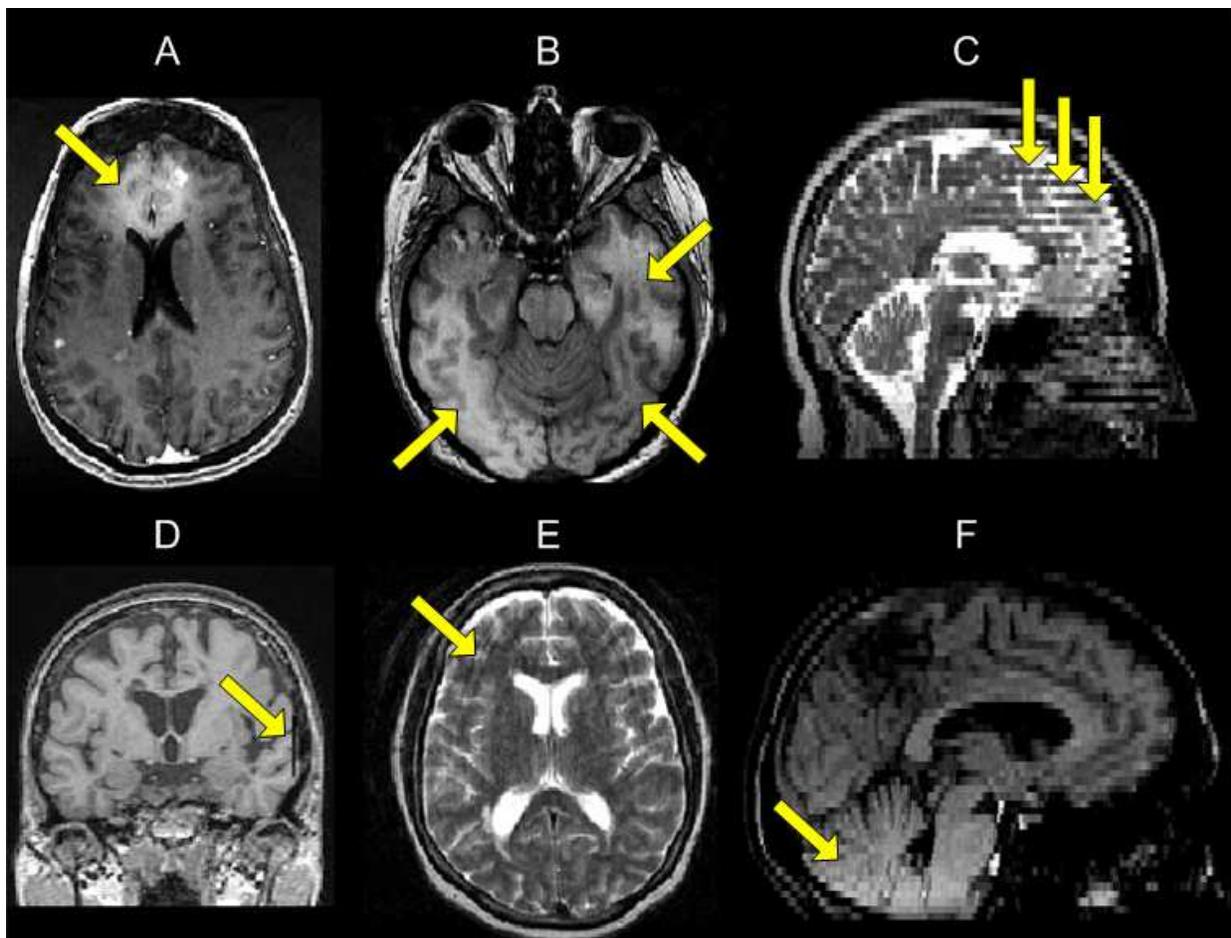

Fig. 3. Shows examples of poor quality MR images with yellow arrows highlighting artifacts: A) T1w+Gd axial slice with hyperintense artifact in the frontal lobes of the brain (caused by mucus in the nasal sinus), B) T1w axial slice with intensity non-uniformity (could not be corrected), C) T2w sagittal slice illustrating interpacket motion artifacts (sharp gradients at the edge of each slice cause by subject movement during multi-shot acquisitions), D) T1w coronal slice showing missing slices, E) T2w axial slice with motion artifacts (ringing in left/ right direction), and F) T1w saggittal slice showing intensity variations in the cerebral cortex

ringing from improper sampling rate or using a small field of view (FOV), conductive objects in the FOV such as braces and tooth fillings, blood flow through major venous structures, or signal dropout from air/ tissue interfaces like the nasal sinus. Fig. 3 shows examples of MRI images that are considered "poor quality" due to the presence of artifacts. These images would be expected to yield incorrect results for many image processing algorithms. While there exists algorithms to correct some of these artifacts (Ahmed et al., 2003; Blumenthal et al., 2002b; Forbes et al., 2001; Greenspan et al., 2001; Kim et al., 1999; Lötjönen et al., 2004; Malandain et al., 2004; Ourselin et al., 2000; Rousseau et al., 2005; Sled et al., 1998; Ward et al., 2000), these corrections may not be adequate to achieve the expected precision of the downstream image processing to quantify brain pathology metrics. Longitudinal inconsistencies tend to result from scanner software and hardware upgrades, scanner hardware deterioration and human errors/ inconsistencies. Fig. 4 shows the effect of inconsistent patient positioning where two same-day scans were acquired, an initial scan (Scan) and repeat scan (Re-scan) after repositioning the patient in the scanner. Fig. 4 demonstrates that simply repositioning a patient and rescanning can result in non-linear changes in brain shape on the rescanned image relative to the initially acquired image that may result in loss of accuracy and precision of MRI-derived metrics. The presence of between-timepoint inconsistencies can be expected to increase the error in brain pathology metrics that compare images acquired at different timepoints (e.g. measuring change in brain volume by comparing the follow-up image to the baseline image) and decrease the power of statistical tests comparing the metrics calculated from images acquired at different timepoints (e.g. determining if there is a statistically significant difference in the volume of WM lesions at follow-up compared to the volume of WM lesions at baseline).

To develop an appropriate quality control procedure for multi-centre clinical trials of therapeutic treatments, image artifacts and longitudinal inconsistencies that affect MRI quality and the evaluation of therapeutic efficacy should be detected and controlled using appropriate tests.
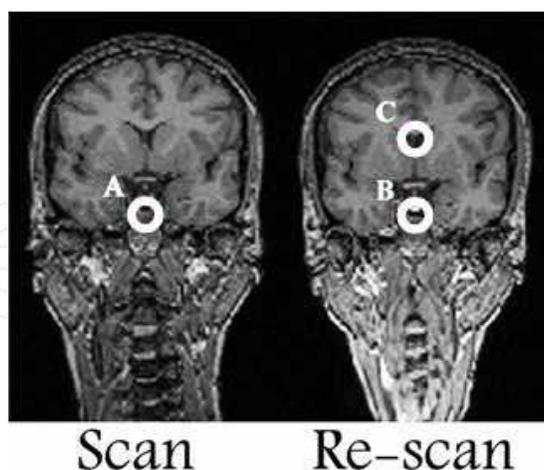

Fig. 4. Shows a scanned image with the magnet's isocenter identified with a circle and labelled A (left) and a re-scanned image with the magnet's isocenter identified with a circle and labelled B (right). The scanned image's isocenter relative to the re-scanned image's isocenter is identified on the re-scanned image with a circle and labelled C. The change in position between both images is illustrated by labels B and C. The distortion between the two images is apparent in the neck and top of the brain
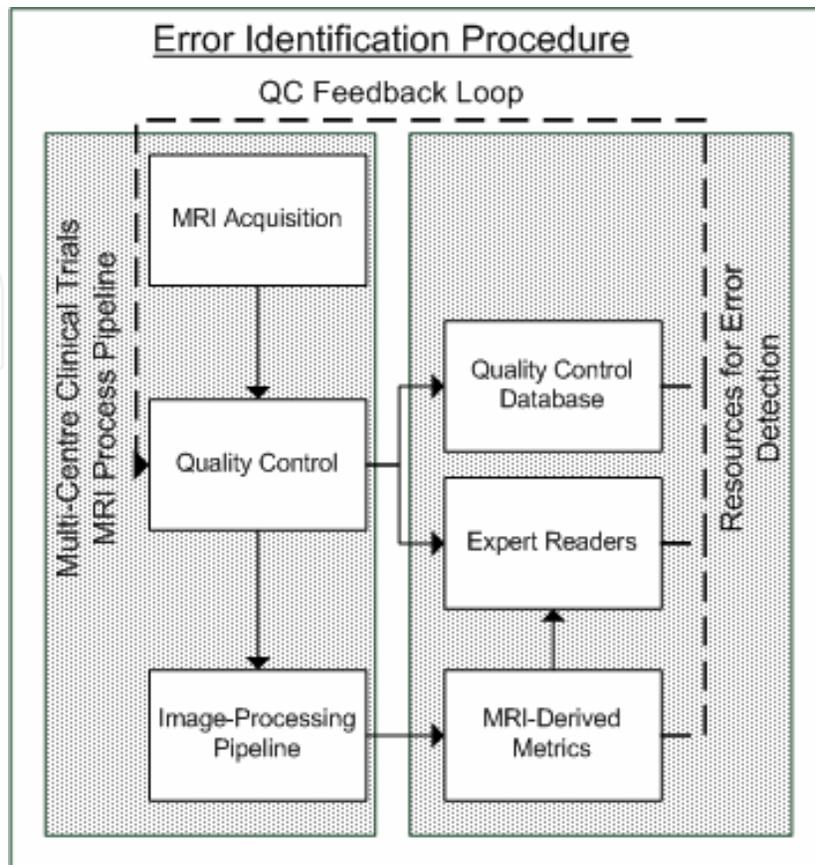
Fig. 5. An error identification procedure that is used to detect poor quality MRIs that may impact MRI-derived brain pathology metrics calculated in multi-centre clinical trials. Expert readers experienced with MRIs, information within the QC database, and MRI-derived metrics are the primary resources used to detect errors. Using a QC feedback loop, those errors are used to ensure that the tests in the QC procedure are current and effective

Determining Important QC Tests

QC tests need to be developed to detect the attributes associated with poor quality MRIs capable of affecting the accuracy and precision of brain pathology metrics. These tests can be determined using a semi-automated dynamic error identification procedure consisting of expert MRI readers, automated quality control systems and databases, and abnormal measurement variations in the MRI-derived metrics (Fig. 5). Expert MRI readers are trained professionals that have experience working on MR images that are affected by pathology and are, therefore, important to the process of identifying errors. MRI readers are an ideal resource to use for screening MRIs for image artifacts and longitudinal inconsistencies because they examine several MRIs daily, are trained to identify the pathology of the neurological disease on MRIs, and are able to distinguish between visual artifacts and expected MRI variations. Automated quality control systems and databases provide access to historical QC measurements that are especially important for identifying longitudinal inconsistencies. For example, the SNR values for serially acquired MRIs could be used to detect scanner changes when the required information in the DICOM header file is unavailable. The error identification procedures described above ensures that QC tests in the QC procedure are current and effective.

Imaging Markers for QC Tests

The QC tests use imaging markers to quantify the attributes associated with poor quality MRI that may affect the accuracy and precision of brain pathology metrics. Imaging markers are MR acquisition references that provide reliable, consistent, and representative information on the performance of the MR scanner and the fidelity of the MRI. Using image processing techniques, pertinent data in the imaging marker are identified and used to measure the level of quality in a MRI. There are three types of imaging markers that are commonly used for quality control: phantoms, external markers, and the MRI itself (normal control subjects and patient data). Consideration should be given to how the availability, feasibility, limitations, advantages, and importance of each imaging marker affects the development of a QC procedure.

An MRI phantom is brain-like in size and shape and fabricated using materials with relaxation properties conducive to MR imaging. Phantoms range from simple structures, like a sphere of agar or bottle of doped water, to more complex designs, like concentric spheres of agar where each sphere has a different concentration of agar solution. The general idea of using phantoms for quality control is that the images acquired of the phantom should be consistent with phantom images obtained at different sites involved in the trial and consistent over time at a given site. Phantoms have been developed by several groups including American College of Radiology (ACR) MRI accreditation program, European Community Concerted Action, National Electrical Manufacturers Association (NEMA), American Association of Physicists in Medicine (AAPM), and Alzheimer's Disease Neuroimaging Initiative (ADNI) (ACR, 2004, 2005; NEMA, 1988, 2001, 2003a, 2003b, 2003c; Price et al., 1990). The use of phantoms in multi-centre clinical trials requires imaging of the phantom at regular intervals using the same sequences approved for the site by the trial's MRI-analysis centre even when scanner hardware and software are stable, and also before and after every scanner-associated upgrade. The limitations of using phantoms for QC include financial and time feasibility of phantom production and repeated scanning, variability in the fabrication procedure and composition of the construction materials (affects site-to-site measurements), degradation of construction material over time (adds errors to longitudinal measurements), and the inability to represent the anatomical structures of real brain MRIs accurately (adds uncertainty to the interpretation of phantom-based measurements in the context of real brain MRIs). The advantage of using phantoms is that ground truth is known which allows for precise measurements of MR scanner performance parameters like geometric accuracy, high contrast spatial resolution, slice thickness accuracy, image intensity uniformity, percent signal ghosting, and the ability to detect low contrast objects. Additionally, phantoms can be used for correcting MRI geometric distortions caused by magnetic field inhomogeneities and gradient nonlinearities in the scanner (Jovicich et al., 2006). This is especially important for MRI-derived metrics that quantify morphological changes of anatomical structures in the brain like changes in cortical thickness, whole brain atrophy, and ventricular enlargement.

External markers for QC refer to small simple objects (e.g. cylinders, spheres) that are placed with the subject at the time of acquisition and fabricated using materials with relaxation properties that produce MR signals when scanned (e.g. tubes filled with manganese chloride or copper sulfate solution). The general idea of using external markers for QC is that they represent known quantities that are scanned under truly identical conditions (i.e. at the same time) as the brain, unlike the phantom that would be scanned in a different session

when the scanner may perform slightly differently. MRI-compatible external markers such as agar are readily available and scanning with external markers is more feasible to implement in multi-centre clinical trials than phantoms since the subject and marker can be scanned simultaneously. As with the phantoms, the properties of the external markers are known, which is useful for tracking morphology and intensity changes over time resulting from MR hardware degradation and software/ hardware changes, or comparing quality control parameters (e.g. SNR, contrast-to-noise ratio) for different scanners at multiple sites. External markers are susceptible to the same limitations as phantoms (i.e. variability in the fabrication procedure and composition of the construction materials, degradation of construction material over time, and the inability to represent the anatomical structures of real brain MRIs accurately). Additional limitations of using external markers for QC include the limited space they occupy that is external to the brain (i.e. cannot detect spatially varying errors within the brain) and the necessity for consistent positioning of the external markers to minimize spatial variability of measurements for QC.

MRIs of either normal control subjects (for QC only) or of the subjects enrolled in the trial can be used as imaging markers to evaluate image quality. The general idea of using human scans for QC is that, unlike phantoms, they represent the actual imaging properties of the brain under the same scanning conditions of the subjects in the trial (e.g. potential for movement, flow artifacts from the carotid arteries). The normal control subjects can be considered as "living phantoms", such that images are acquired regularly with identical sequences as prescribed by trial protocol, but not under the identical conditions as each individual patient. Unlike the man-made-phantom images, the ground truth of the normal control subject images is not known, but the biology is assumed to be stable and normal. The MRIs acquired from the subjects enrolled in the clinical trial may itself be used for QC. Despite the fact that the assumption of stable and normal biology cannot be made, QC may be performed using image characteristics that would not be changed by the presence of pathology. The advantages of using the MRIs acquired for the purposes of the trial are that 1) all scans for each modality are readily available, and 2) the measured QC parameters are indicative of the quality of the image from which the brain pathology metrics will be calculated. Since the ground truth of these images is not known, the QC strategy involves setting control limits for acceptable/ unacceptable MRIs by analyzing the effect of varying QC parameters on MRI-derived metrics. For example, to define the control limit for assessing the effect of MRI motion artifacts on hippocampal volume measurements, a quantitative test can be performed by simulating MRI images with different amounts of motion artifact, calculating the hippocampal volume on these simulated images, and observing the relationship between the error in hippocampal volume and the amount of simulated motion. The control limit of MRI motion artifact for hippocampal volume measurement is thus determined as the maximum amount of motion on an MRI that can yield measurements with similar accuracy and reproducibility as the same MRI with no motion artifact.

The cost of using phantoms or normal control subjects for QC is prohibitive in many clinical trials. External markers may also be considered unfeasible, due to the additional scanning time cost associated with the placement of the markers, and analysis centre costs associated with developing image-processing tools to accommodate their presence and perform a trial-specific set of QC tests. These feasibility issues support the use of imaging markers extracted from the MRIs acquired on the subjects enrolled in the trial to measure QC parameters for quantifying, testing, and assessing image quality.

Degree of Worth of the MRIs

Determining the degree of worth of the MRIs is important because it allows us to differentiate MRIs based on levels of quality. Qualitatively, the degree of worth of the MRIs can be defined as the fidelity of an image to convey the true physiology or pathology of the subject being analyzed that is free from artifacts that could reduce the sensitivity of any MRI-derived brain pathology metric used to determine the effect of treatment on disease. MR images that have artifacts or low SNR that affect the reliability of image-processing algorithms used to quantify brain pathology metrics are considered to be poor quality. MR images that are relatively free of artifacts with acceptable SNR are considered good quality and are expected to yield brain pathology metrics that provide an accurate representation of the expected physiology and pathology.

The degree of worth of the MRIs can be determined using experienced expert MRI readers and quantitative experiments. Experienced expert readers review and analyze large volumes of MRIs, are involved in calculating MRI-derived brain pathology metrics, have knowledge on the MRIs that helped produce the derived brain pathology metrics and, accordingly, are able to assess the effect of image quality on the evaluation of metrics. These qualitative assessments can be coupled with QC test measurements to quantitatively evaluate the degree of worth of MRIs (described in the next section). Optimally, quantitative experiments that evaluate the effect of varying select QC parameters on MRI-brain pathology metrics (e.g. quantifying the effect of MRI noise levels on measuring whole brain atrophy) should be used to determine the degree of worth for each acquired MRI because these methods provide an accurate assessment of deviations in image quality on measurement error. Increases in MRI-derived brain pathology measurement errors decrease the degree of worth of the MRI and vice versa. Unfortunately, quantitative experiments are time consuming (i.e. require several steps including design, development, testing, validation, and verification), may not reflect the true image quality properties (i.e. simulated noise used to modulate SNR may be inaccurate), and difficult to incorporate in dynamic environments such as multi-centre clinical trials (i.e. time required to implement QC tests based on experimental results may be impractical since the solutions to the identified QC errors need to be incorporated promptly).

Creating Control Limits to Assess (Pass and Fail) MRIs

As previously mentioned, automated quality control for MRI brain images require control limits to define the boundary between acceptable and unacceptable MRIs based on image quality and the sensitivity to image quality of the brain pathology metric to be calculated. Control limits can be determined using receiver operating characteristic (ROC) curves, quantitative evaluations of MRI quality parameters on MRI-derived brain pathology metrics, and a set deviation from the expected value of QC parameters.

ROC curves can be used to depict the sensitivity of QC tests by comparing true positive rates (i.e. the number of MRIs that fail QC when they should actually fail) and false positive rates (i.e. the number of MRIs that fail QC when they should not fail) for a range of thresholds; truth tables may be computed if there is a gold standard. MRIs that have been evaluated either qualitatively by experienced readers (e.g. low, medium, high) or quantitatively by image-processing can be used as a gold standard. The reader evaluations can be combined with QC test measurements to generate ROCs and determine optimal image quality control limits. If reader evaluations do not exist, ROCs can also be

determined using datasets where ground truth is known. For example, a MRI dataset consisting of few subjects with multiple acquisitions could be used to determine the control limits for detecting similarity of MRIs (useful to detect patient identification errors). A limitation of using ROCs based on truth tables computed using the qualitative assessments of expert readers is that the derived control limits are prone to human bias and variability.

Control limits can be determined using quantitative evaluations such as varying select image quality parameters (e.g. SNR, consistency of patient positioning) on MRI-derived brain pathology metrics (e.g. lesion volume, cortical thickness) to evaluate measurement error based on changes in MRI quality. As described earlier, the relationship between the computed value of an MRI quality parameter and the brain metric error can be used to establish a control limit reflecting tolerance of low quality only in the context that it does not result in significant brain metric error or reduced reproducibility.
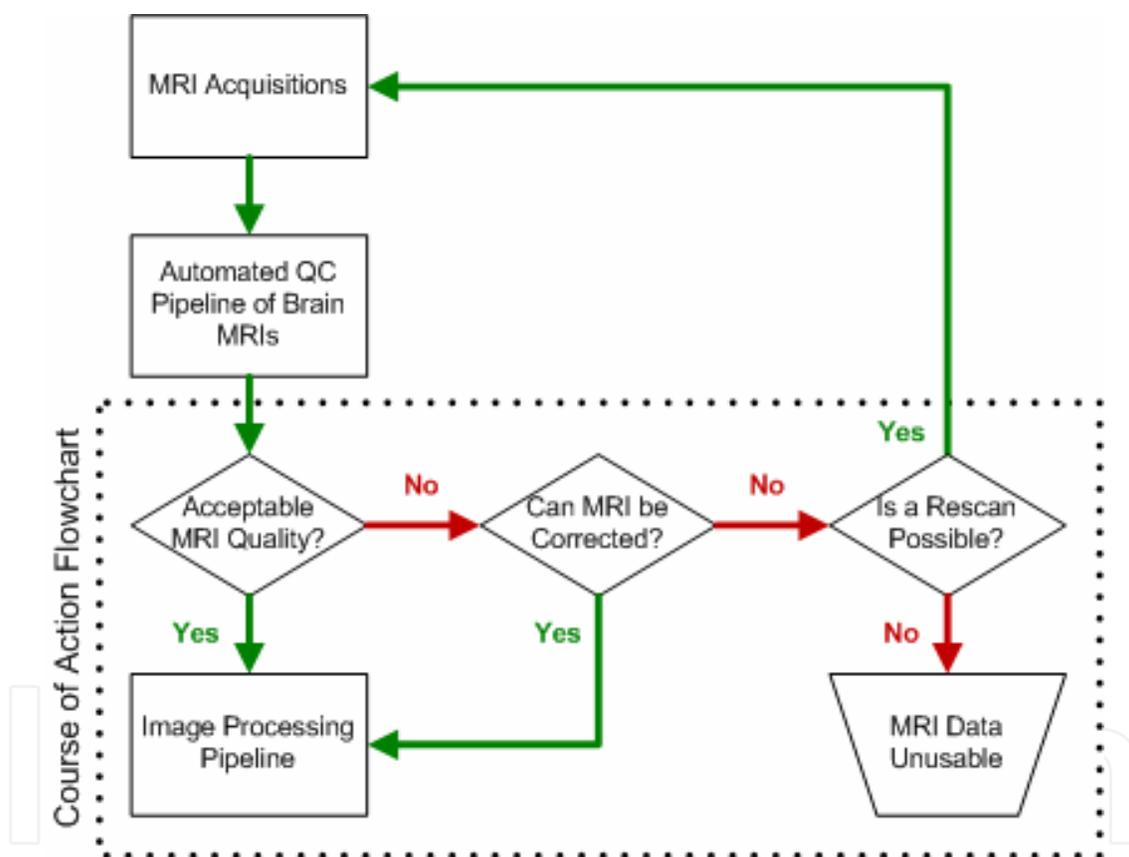
Fig. 6. Shows a QC course of action flowchart for MRIs acquired during multi-centre clinical trials for therapeutics of neurological diseases. After brain MRIs have been acquired, they are assessed for quality using an automated QC pipeline. Images that have acceptable quality progress to the image processing step where MRI-derived brain pathology metrics are calculated. MRIs that do not meet the criteria for acceptable image quality are assessed for correctability. If a correction procedure is available, MRIs are corrected and transitioned to the image processing pipeline step. If MRIs cannot be corrected, the possibility of a re-scan is investigated. In cases where the subject cannot be re-scanned the MRI data is deemed unusable. If a re-scan is possible, the newly acquired MRIs are processed using the same procedure described

Control limits can also be defined as a deviation from an expected value, which is useful for QC tests that check variables that should be constant like trial-, site-, and subject- specific acquisition protocols and sequences protocols (e.g. echo time, repetition time). Although exhaustive testing could be used to determine the effect of small deviations from acquisition parameter values like echo time (TE) or repetition time (TR) on image quality (as large deviations would be considered a breach of the approved protocol), the number of combinations required (scanner make x scanner model x software version x hardware upgrades x sequence) to perform this type of analysis makes exhaustive testing unrealistic. Instead, control limits can be defined as the expected trial-, site-, and subject- specific acquisition/ sequence protocol values plus a deviation to address inherent hardware limitations (e.g. MR scanner incapable of precisely applying user selected parameter values) and differences between expected parameter values manually logged in the QC database and acquired parameter values in the DICOM header files (i.e. due to rounding errors). The deviation from the expected parameter value can be set using hardware specifications, suggestions from experienced MRI readers, analysis of QC database. As an example, the control limits of acquisition echo times could be set to TE ± 1% meaning that MRIs acquired with a measured echo time within 1% of the expected TE are considered acceptable. The deviation amount from the expected value is generally not determined using quantitative approaches and, consequently, should be set conservatively to not introduce QC errors. The aim is to ensure that the specified sequences and protocols that should have been applied were actually applied while accommodating for small variations.

Determining a Course of Action: Accept, Correct, or Reject MRIs

Once control limits for image quality are established for each test in the automated QC pipeline, they can be used to classify MRIs as either acceptable or unacceptable and an appropriate course of action can be determined (Fig. 6). MRIs with acceptable image quality progress to the image processing step where MRI-derived brain pathology metrics are calculated. MRIs that are unacceptable are reviewed by experienced readers and image-processing engineers to determine if correction procedures can be applied. MRIs that can be fixed (e.g. Fig. 3C interpacket artifacts, Fig. 3F bias field, and Fig. 4 geometric distortion) are corrected and transitioned to the image processing pipeline step where brain pathology metrics are calculated. If MRIs cannot be corrected, a MRI physicist may be consulted to determine if scanner hardware failure may be a factor, and the site will be contacted to discuss any hardware issues and the possibility of rescanning. In cases where the subject cannot be re-scanned (e.g. physical limitations, previous re-scans did not improve the MRI quality, situational circumstances) the brain metric is declared unusable. If a re-scan is possible, the newly acquired MRIs are processed using the same procedure described. Note that there are many attempts to achieve reproducible and accurate brain pathology metrics and that even if the MRI data is not adequate for the calculation of one metric it may still be of adequate quality to yield other metrics that are accurate and reproducible.

5. QC procedure for brain MRIs acquired in multi-centre MS clinical trials

The framework described in this chapter was used to create an automated quality control (aQC) procedure for brain MRIs acquired in multi-centre clinical trials for MS (Fig. 7). The aQC pipeline was composed of eight QC tests designed to increase the fidelity of MRI-derived brain pathology metrics by preventing unacceptable images from being processed.
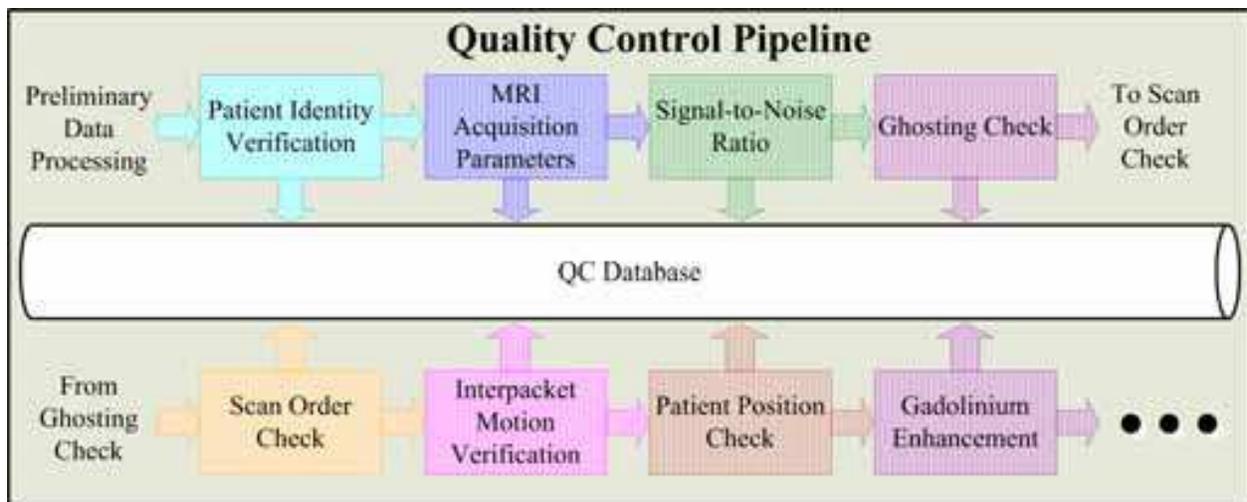
Fig. 7. Illustrates a quality control pipeline consisting of a series of eight tests designed, developed, tested, and validated for brain MRIs acquired in multi-centre clinical trials for MS. QC results and pertinent data for each test are recorded into a database and used for error checking and verifying consistency between serial acquisitions. The pipeline's efficiency can be attributed to a preliminary data processing step that optimizes operations that are shared between most QC tests. This pre-processing step minimizes the use of redundant QC test operations
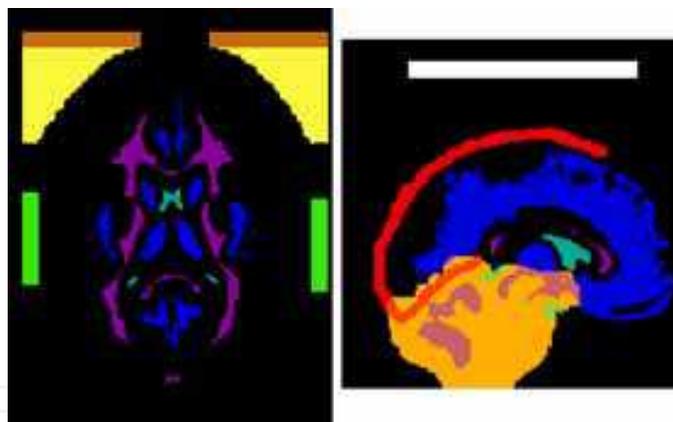
Fig. 8. Shows a 2D axial slice (left) and sagittal slice (right) of the unified QC template in standard space with noise regions in orange, yellow, green, and white, WM in purple, GM in dark blue, CSF in light blue, cerebellum in dark yellow, and sagittal and straight sinus in red. The other colors are indicative of ROIs that overlap with the cerebellum

The QC test suite includes patient identity, MRI acquisition parameters, signal-to-noise ratio, ghosting, gadolinium enhancement, scan order, interpacket motion, and patient position verification; each test was identified using the error identification procedure described in section 4.3 (Fig. 5) and utilized MRI-based imaging markers and DICOM header files to measure test-specific indicators of quality (e.g. WM masks for SNR calculations, sagittal and straight sinus masks to determine if sufficient gadolinium enhancement was achieved, background noise masks to detect ringing artifacts, comparison of acquisition parameters in the DICOM header file to the requested parameters to ensure

proper protocols were followed). All MRI-based imaging markers needed by the QC pipeline were consolidated into a single unified QC template (Fig. 8). Ordinarily, separate anatomical and/ or background ROI would be created in a standard coordinate space (e.g. MNI-space) for each QC test and used to calculate MRI-based QC measurements (e.g. WM mask for SNR measurements). Unfortunately, this would require each ROI to be registered separately, thus, increasing the processing time of the pipeline. Using a unified QC template minimized the number of redundant operations used by each QC test and increased the overall efficiency of the pipeline. The template consisted of a superior, anterior, and lateral noise region of interest (ROI) for ghosting (Fig. 8 – white, orange, and green respectively), frontal noise ROI for SNR (Fig. 8 – yellow), sagittal and straight sinus ROI for gadolinium enhancement (Fig. 8 – red), and WM, GM, and CSF samples for SNR verification (Fig. 8 – purple, dark blue, light blue). The unified QC template was created in a standard coordinate space (MNI-space) using manually labelled ROIs (e.g. background noise and sagittal and straight sinus) and MNI-space anatomical probability maps (Mazziotta et al., 1995), tissue maps based on large sample sizes that indicate the probability of a specific tissue type being at a particular anatomical location in the image (e.g. WM, GM, and CSF). A quality control database was used to store quantitative (e.g. measured indicators of quality for each test performed) and qualitative (e.g. pass and fail flags indicating the outcome of the QC pipeline and each individual test) data as well as pertinent acquisition information found in the MRI DICOM header files (e.g. parameters used to acquire each MRI, scanner make and model, software revision). The QC database was also used for error tracking and comparing QC results from serial acquisitions for consistency. Independent sample sets populated with MRIs affected by various levels of image quality were used to train and validate each QC test, while experienced expert MRI readers and metric-based quantitative experiments were used to determine the degree of worth for each MRI. Control limits were established using ROC curves, quantitative evaluations of MRI indicators of quality on MRI-derived brain pathology metrics, and specific deviations from the expected measurement value of QC parameters. While details on the methods for each QC test has been previously described (Gedamu et al., 2008a; Gedamu et al., 2008b; Gedamu et al., 2008c), a brief description of each test procedure found in the pipeline is provided below.

Quality Control Tests

Patient Identity Verification: In clinical trials, longitudinal data often is acquired from the same subject over the course of the trial. Occasionally, such scans are incorrectly labelled, e.g., as coming from a different subject. The patient identity verification procedure verifies that serial images supposedly acquired from the same patient actually contain images of the same brain and that cross-subject MRIs within a site are unique (i.e. no two subjects have the same brain). For same-subject serial acquisitions, T1w extracted brains from two consecutive timepoints are registered together and a cross-correlation coefficient value is used to assess the similarity between both images. To ensure that cross-subject MRIs are unique within a site, the initial scans of new subjects are compared to the initial scans of all other subjects within their site using the same registration method used to verify the integrity of serial acquisitions.

MRI Acquisition Parameters Verification: In a clinical trial, it is important for data to be acquired consistently according to a pre-specified protocol in order to ensure comparability of data acquired at different sites and over time. For example, changes in echo times (TE) or

repetition times (TR) can affect images contrast, and in turn, may modify the results of a tissue classification procedure. Verification of MRI parameters ensures that the acquisition values approved during site qualification, which are generally chosen to achieve consistent image characteristics for analyses, are respected. This is achieved by comparing the approved parameters that are stored in a QC database (i.e. populated during site qualification) against the received parameters recorded in the image DICOM header file.

Signal-to-Noise Ratio Verification: The processing of an image can be substantially influenced by the signal to noise ratio (SNR). The noise levels of MRIs can obscure anatomical and pathological borders between different tissue types (e.g. lesion/ WM, GM/ WM, lesion/ CSF borders) thereby affecting the reliability of registration, classification, and segmentation procedures. The SNR verification procedure ensures that each acquired MRI is within an acceptable limit. SNR can be determined by dividing the tissue type with highest mean intensity, either WM or CSF (Fig. 8 – purple and dark blue respectively), by the standard deviation of the background noise (Fig. 8 – yellow) which has been compensated for Rayleigh distribution effects.

Ghosting Verification: Head movement during MRI examinations is a very common source of artifact, which generally appears as ringing or "ghosting" artifacts (Fig. 3E). Ring-like structures (aliasing), a characteristic trait of ghosting, produce non-uniform intensities within the brain and in the surrounding background. Consequently, confidence in anatomical borders is compromised, and the ability to discern different tissue types and pathology (e.g. lesions) decreases because the intensity coherency within each tissue type is perturbed. Ghosting artifacts can be detected by comparing the standard deviation of two independent noise regions. For 2D multi-slice acquisitions the anterior region (Fig. 8 – orange) and the left and right side of the head (Fig. 8 – green) are compared. For 3D global acquisitions the superior (Fig. 8 – white) and anterior (Fig. 8 – orange) regions are compared.

Scan Order Verification: In clinical trials, multi-modal MRIs are acquired for each subject at each timepoint (Fig. 2 – MRI Acquisition) and it is important to ensure that the order, time, and date of each modality are correct and consistent according to a pre-specified protocol. MRI modalities that should have been acquired during a single scan session but were acquired over multiple days (e.g. T2w/ PDw images that were acquired days after a T1w image was acquired) could be affected by pathological/ biological (e.g. appearance of a new lesion) or systemic variability (e.g. changes in patient positioning that cause geometric distortion artifacts) which could affect the reliability of brain pathology metrics. Acquisition order can be determined by comparing the approved scan order protocols that are stored in a QC database (i.e. populated during site qualification) against the actual scan times recorded in the image DICOM header file.

Interpacket Motion Verification: Inter-packet motion artifacts (Fig. 3C) are associated with subject movement during an interleaved multi-slice MR imaging sequence, a specific type of sequence where multiple 2D MRI sets, termed packets (Fig. 9 – illustrates three packets painted in green, blue, and purple), are used to construct full 3D MR volumes. Fig. 9 illustrates the effect that interpacket motion artifacts can have on MRI-derived brain metrics where three packets were acquired with the first, second, and third packets shown in green, purple, and blue respectively. Packet 1 is acquired with the brain initially rotated slightly clockwise, packet 2 is acquired with a larger rotation in the counter-clockwise direction, and packet 3 is acquired after the brain undergoes a small translation in the axial direction. The final reconstructed MRI (right) shows the effect of motion between each acquired packet as regions of missing (areas where the packets do not cover the image) and redundant data

(areas where multiple packets cover the same regions). This impedes the MRI from conveying the complete anatomical and pathophysiological structures in the scanned brain and can introduce errors in subsequent MRI-derived brain metrics. This type of artifact can be determined by measuring out-of-plane motion, movement between 2 or more packets that causes missing data, and in-plane motion, movement between 2 or more packets that cause structural misalignment between 2D slices but does not result in missing data (Gedamu; Gedamu; Collins & Arnold, 2008c).
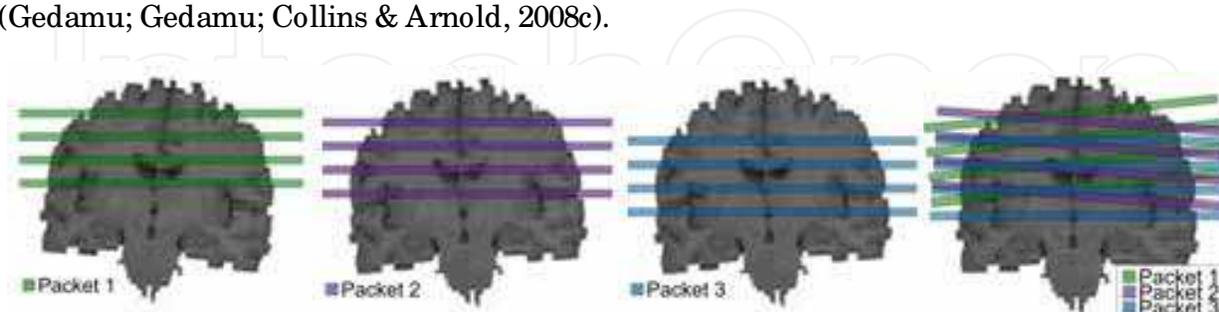
Fig. 9. Packet 1 is acquired with the brain initially rotated slightly in the clockwise direction (left), packet 2 is acquired with a larger rotation in the counter-clockwise direction (middle left), and packet 3 is acquired after the brain undergoes a small translation in the axial direction (middle right). The image on the right shows the result of registering all packets together. Notice the missing data (areas where the packets do not cover the image) resulting from motion between packets during acquisition

Patient Position Verification: Magnetic field inhomogeneities and gradient nonlinearities can alter the volume of anatomical structures in MRIs (termed geometric distortion) based on the placement of the subject in the scanner (Fig. 4). In multi-centre clinical trials, the position of the subject should be consistent for each scan and the centre of the subject's brain should be aligned with the magnet's isocenter (i.e. location least affected by geometric distortion) to minimize distortion artifacts. Subject positioning is usually approximated by aligning the center of the eye with the center of the magnet. To verify proper subject positioning during image acquisition, MRIs were registered to an average brain in standard coordinate space (MNI-space) because the center of the average brain and magnet isocenter of each MRI have the same x,y,z location, coordinates (0,0,0). Accordingly, misalignments between the center of each MRI and the magnet's isocenter were reflected in the registration transformation matrix. Deviations in the transformation matrices were also used to verify the consistency of a subject's position for serial acquisitions.

Gadolinium Enhancement Verification: In scans that require quantification of gadolinium enhancement, for example, of MS lesions, it is important to ensure the proper amount of gadolinium was injected, the scan was acquired after an appropriate delay, and the post-contrast images show appropriate enhancement of normal structures, such as blood vessels. Appropriate gadolinium enhancement was done by comparing the signal intensity of large venous structures like the sagittal and straight sinus (Fig. 8 – red) in pre and post gadolinium MRIs while the time delay between the pre-/ post- contrast image acquisitions were determined using the recorded scan times in each image's DICOM header file.

QC Pipeline Optimization

Prior to running each QC test, a preliminary data processing step (Fig. 7 – Preliminary Data Processing) was done to consolidate time-consumptive operations that were redundant

across most QC tests into a single operation which was shared among all tests (minimize cross-test redundancies). The preliminary data processing step comprised of using a standard registration procedure to align the unified QC template (Fig. 8) to each MRI modality that was acquired during MRI acquisition (Fig. 2 – MRI Acquisition), measuring important statistical data for each MRI modality in the regions defined by the registered unified QC template, and storing the measured statistical data and transformation matrices obtained from the registration procedure into the QC database. The standard registration procedure (Fig. 10) was performed by selecting a reference MRI among the acquired MRI modalities (e.g. T1w), calculating a transformation matrix to align a brain model in MNI-space to the selected reference image in the subject's native coordinate space, calculating a transformation matrix to align the reference MRI to the other MRI modalities (e.g. T1w-to-T1w+Gd, T2w, PDw, and FLAIR), and concatenating the transformation matrix between
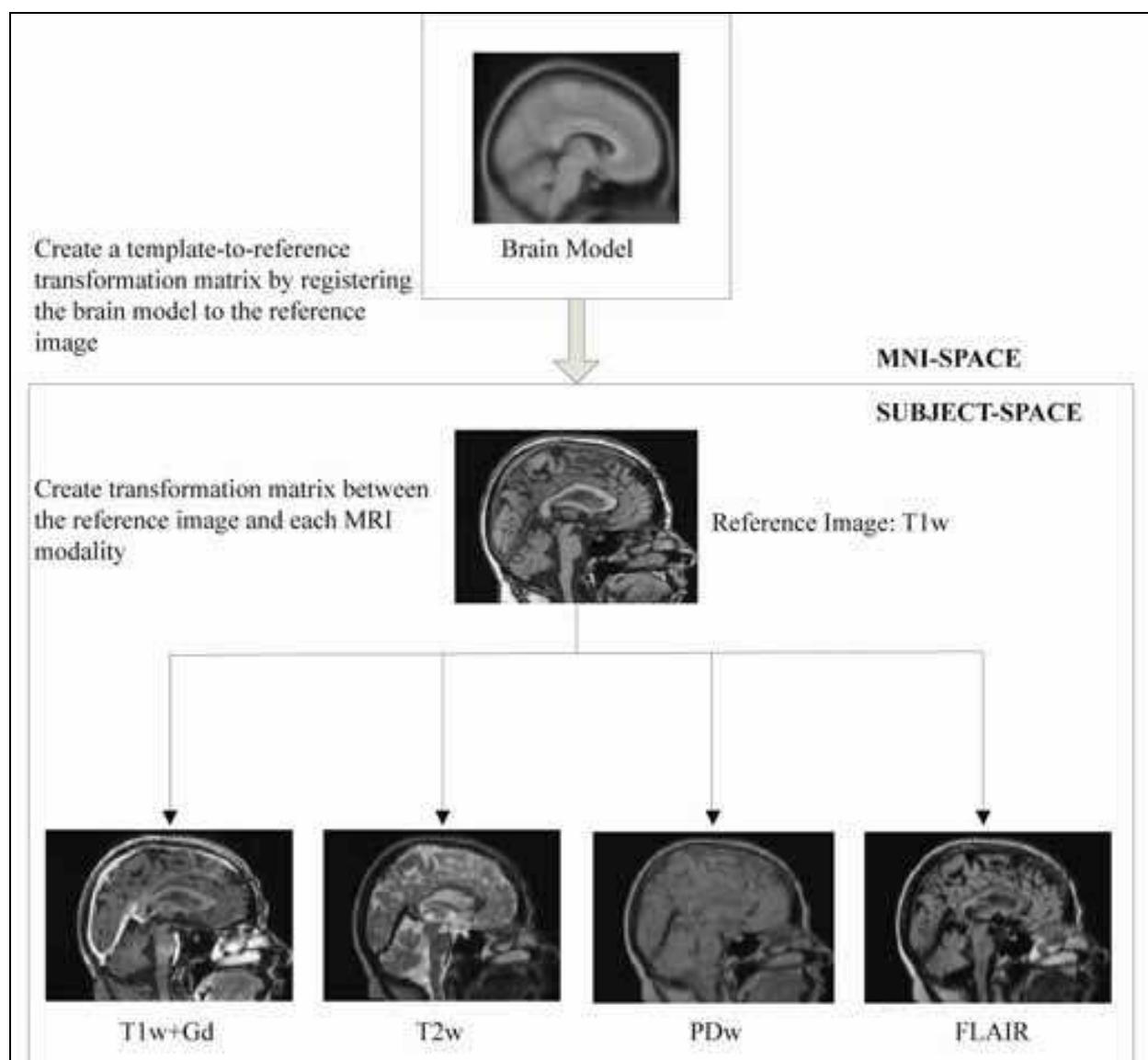
Fig. 10. Standard registration protocol used to calculate a set of transformation matrices between standard coordinate space and each modality (T1w, T1w+Gd, T2w, Pdw, and FLAIR)

the two alignments to create a set of modality-specific transformation matrices (e.g. brain model-to- T1w+Gd, T2w, PDw, and FLAIR). An MNI-space brain model, instead of the MNI-space template itself, was used to determine the transformation matrix between MNI-space and the subject's native space because the registration process requires images with similar attributes to function correctly. A T1w reference image was used because T1w images are generally acquired for clinical trial studies, making them readily available, and the brain model was T1w, which maximized the similarity between the images. The template was registered to each MRI, as oppose to aligning each MRI to the template, to ensure QC measurements were made using the original MRI data (i.e. not affected by interpolation of image data that occurs during the registration procedure). By calculating a set of transformation matrices once, in contrast to performing the same registration procedure for each test in the pipeline, reduced the number of redundant operations and increased the overall speed of the pipeline, which enabled quicker MRI quality assessments.

To accommodate for growth, the quality control procedure was designed as a series of modularized tests allowing new tests to be designed, developed, tested, and validated independently before being added to the QC pipeline. To address concerns of scalability, the pipeline was designed to minimize its load effect (i.e. number of read/write accesses) on the central MRI database. This was achieved by using computer servers to perform QC analyses locally. Essentially, the MRI database is accessed once, instead of multiple times during the course of the QC analyses, to copy all the necessary MRI data to a computer server where the QC pipeline will be run (local processing). This limits the chance of overloading the MRI database with multiple read/write accesses which could result in slow response times or even crashes (non-responsive database). Performing quality control procedures locally using server systems (i.e. copying the required MRI data locally) reduced the load on the database, increased the number of potential processing systems (i.e. 'N' possible local computer servers), and, accordingly, increased the amount of MRIs processed.

6. Conclusions

In this chapter, guidelines were provided for developing an appropriate automated QC procedure for brain MRIs acquired in multi-centre clinical trials of therapeutics for neurological diseases. In addition, these guidelines were applied to develop an aQC procedure specific to multi-centre clinical trials for MS consisting of eight QC tests (patient identity, MRI acquisition parameters, SNR, ghosting, gadolinium enhancement, scan order, interpacket motion, and patient position verification). The procedure has been applied to large scale multi-clinical trials and increased the fidelity of MRI-derived brain pathology metrics by preventing unacceptable images from being processed.

7. Acknowledgments

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