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Review Article

Neuroimaging Considerations for Studying Post-Operative Cognitive Decline

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Abstract

The mechanisms and etiology of post-operative cognitive decline (POCD) are not well understood. POCD is common in older adults undergoing major surgery, particularly following cardiac and orthopedic procedures. Brain reserve, defined as the ability of individuals' brains to cope with insults and pathology, might account for differences in cognition following major surgery. Neuroimaging tools allow for the assessment of individual brain reserve and have the potential to provide insights into the etiology of POCD. Here we present a brief summary of standard clinical and more advanced neuroimaging sequences warranting consideration for clinical research studies addressing POCD. Standard brain MRI protocols useful for understanding POCD include.

T1, T2, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). While two-dimension (2D) acquisitions are common clinically, three-dimension (3D) sequences are advised for research purposes in order to advance clinical science. In addition, the inclusion of advanced 3D MRI acquisitions such as DTI and resting state functional MRI is critical for the detection of more subtle and or functional disturbances causing POCD. Such advanced MRI techniques will facilitate the understanding of the etiology of POCD, will be able to better predict and manage patient's outcomes and ultimately improve patient's care.

ABBREVIATIONS

POCD: Post-Operative Cognitive Decline; FLAIR: Fluid-Attenuated Inversion Recovery; DWI: Diffusion-Weighted Imaging; MRI: Magnetic Resonance Imaging

INTRODUCTION

While considerable clinical research has been conducted on post-operative cognitive decline (POCD), the mechanisms and etiology of POCD are not well understood [1,2]. Despite numerous attempts to identify anesthetic or surgical mechanisms for operative related cognitive decline, there are no definitive conclusions to date. General anesthesia remains an unconfirmed influence on cognitive decline per randomized studies [3-5], despite animal studies suggesting that inhalational anesthetics enhance oligomerization and cytotoxicity of amyloid β peptides (a protein change associated with Alzheimer's Disease [6], tau phosphorylation [7], and associate with neuroinflammatory response in humans [8]. Surgical related mechanisms remain inconclusive. As a result, multidisciplinary teams that include anesthesiologists are beginning to address how individuals' brain integrity prior to surgery with anesthesia contributes to cognitive vulnerability around the time of surgery and how brains change pre to post surgery. Research rationale is at least partially based on the brain or cognitive reserve hypotheses.

Reserve establishes a critical threshold of cognitive function until some combination of factors (e.g., brain damage, neuronal stress) accelerates symptom manifestation [9]. Individuals might have certain amounts of brain pathology but due to brain reserve, cognitive impairment will only manifest once a combination of stressors reduces reserve below a certain threshold [9-14]. For POCD, these stressors may include perioperative events such as surgical anxiety, pain, hypoperfusion, or anesthesia.

Neuroimaging techniques can be used for the assessment of individual brain reserve [15,16]. Magnetic resonance imaging (MRI) tools allow us to quantify brain regions, to determine the extent of diseases prior to surgery, and to assess for changes post-operatively. Certain markers of disease state, such as specific areas of cortical atrophy or evidence of cerebrovascular disease, may be valuable indicators of surgical risk [14]. MRI tools are also useful for pre- to post-operative monitoring of cerebrovascular

strokes – both clinical and 'silent' strokes – which have been associated with POCD [17,18].

Here we present a brief summary of standard clinical and more advanced neuroimaging sequences warranting consideration for clinical research studies addressing POCD in adults. We summarize the basics of MRI physics, applicable standard clinical sequences, and finish with more advanced MRI methods.

SUMMARY OF MAGNETIC RESONANCE IMAGING

Magnetization induced in the human body by an external magnet forms the physical basis of MRI. The degree of magnetization generated in an anatomical structure is contingent upon its proton density, which in turn depends upon the number of hydrogen atoms.

Therefore, fluids will have the highest magnetization properties with cortical bone having the lowest. When a patient is placed into the magnet, all protons within the patient's body align longitudinally with the main field of the scanner (also known as longitudinal magnetization). The longitudinal magnetization cannot be measured, so during an imaging sequence the protons are 'knocked out' from their longitudinal alignment. This process generates transverse magnetization, which can be measured as an 'echo' that is expressed as signal intensity. After the 'knock out', protons immediately attempt to realign with the main magnetic field with the realignment taking varying amounts of time depending on tissue composition. As the protons realign with the main field, the transverse magnetization decreases and the longitudinal magnetization increases [19].

MRI protocols include a set of MRI sequences that vary in: Repetition time (TR): TR is defined as the time between the different 'knock outs'. A higher TR increases time protons have to realign with the main magnetic field and to recover the longitudinal magnetization.

Echo time (TE): TE is the time between the 'knock out' and the reading of the echo. Shorter TEs result in higher numbers of 'knocked out' protons and subsequently higher transverse magnetization.

Flip angle: expresses the degree of 'knocking out' of the protons. Spin echo sequences apply a 90 degree flip angle while gradient echo sequences utilize <90 degree flip angles. Higher flip angles result in greater transverse magnetization and increased signal intensity. Therefore, spin echo images are of better quality than gradient echo images at the expense of markedly longer acquisition time. Gradient echo images, while quicker to acquire, are also prone to susceptibility artifacts, which further influence the image quality.

Following is a description of basic sequences used to study gray and white matter composition of the brain.

Standard clinical sequences

T1- weighted images provide the best anatomical detail of all sequences and are often referred to as 'anatomy scans'. T1-weighted images have short TR and TE. Such parameters enhance the differences between the various water heavy tissues (such as cerebrospinal fluid [CSF] or vitreous) appearing with dark signal and fat-based tissues (such as myelin or subcutaneous fat) appearing as very bright signal (Figure 1). T1-weighted images can be obtained as a spin echo or gradient echo sequence. Utilization of the gradient echo technique shortens the acquisition time but is more prone to artifacts that might be mistaken for lesions. In particular, flow-related artifacts are diagnostically problematic as they may cause spontaneously bright signal on unenhanced T1 images that can be mistaken for thrombosed vessels or suggest enhancement that is actually not present. Therefore, spin echo imaging is often the preferred sequence with gradient echo sequences primarily reserved for uncooperative patients or when brief imaging is necessary.

T1-weighted scans allow for segmentation of brain structures that might be particularly prone to atrophy or perioperative insults. For example, structures highly involved in memory (e.g., entorhinal, hippocampus) can be 'segmented' using hand drawn methods [14,20] or with automated approaches [21]. Researchers are encouraged to pay attention to the white and gray matter contrasts acquired from their scanner and obtain thin section volumetric acquisitions so that appropriate segmentation of anatomical regions can be performed. Depending on the structure and scanner used, two of these sequences may be needed for accurate segmentation and motion correction [22].

T2-weighted images allow for clear delineation of fluid from soft tissues. T2 weighted images result from long TR and TE. This leads to the very bright signal of water-based tissues (Figure 1). In contrast to T1 images, gradient echo technology is preferred for T2- weighted imaging because the spin echo sequence has significantly longer acquisition time predisposing the images to motion degradation. T2 images are often preferred for visual assessment of brain atrophy because the CSF is bright, offering excellent contrast to the dark brain tissue. T2 images are also useful for visualizing lacunae, which are one manifestation of ischemic stroke; lacunae will appear as an area of very bright signal and, as a marker of cerebrovascular disease, could contribute to cognitive outcome following surgery [14,17,18]. In addition, T2-weighted sequences best demonstrate pathology since many diseased tissues show edema related to accumulation of fluid. Therefore, the T2 image set is often called the 'pathology scan'. T2* gradient echo is a special T2-weighted sequence that needs to be acquired separately from T2 images. T2* accentuates magnetic field heterogeneities and is therefore recommended for visualization of microbleeds within the brain substance, which appear as small areas of signal loss, also called "black dots". Existing microbleeds can be related to chronic hypertensive encephalopathy or to amyloidosis and are associated with future intracerebral hemorrhage and cognitive decline [23]. Therefore, these represent important indicators of brain health and might be able to predict POCD. Fluid-attenuated inversion recovery (FLAIR) images are similar to T2-weighted images as they are optimized to detect edema. Unlike T2 images, however, the signal from CSF is suppressed, resulting in dark appearances of the CSF within the ventricular system, the sulci over the convexities, and cisterns (Figure 1). The CSF suppression makes acute to subacute subarachnoid hemorrhage as well as cortical blood products more apparent on the FLAIR images, which would otherwise blend together with the hyperintensity of CSF on the T2 images. In addition, the FLAIR sequence can be used to detect small vessel

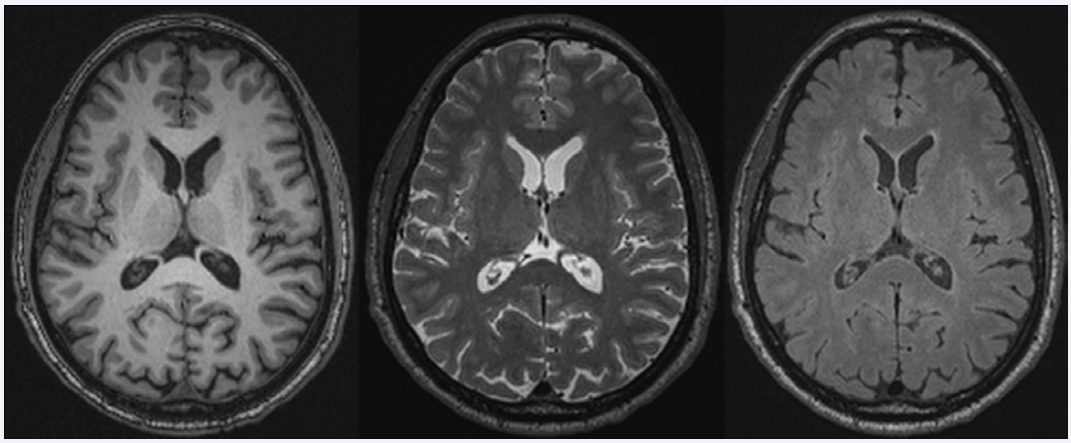

Figure 1 MRI Sequences of an Older Adult Brain
T1, T2, and FLAIR images (respectively) from a healthy older adult with little evidence of brain pathology.

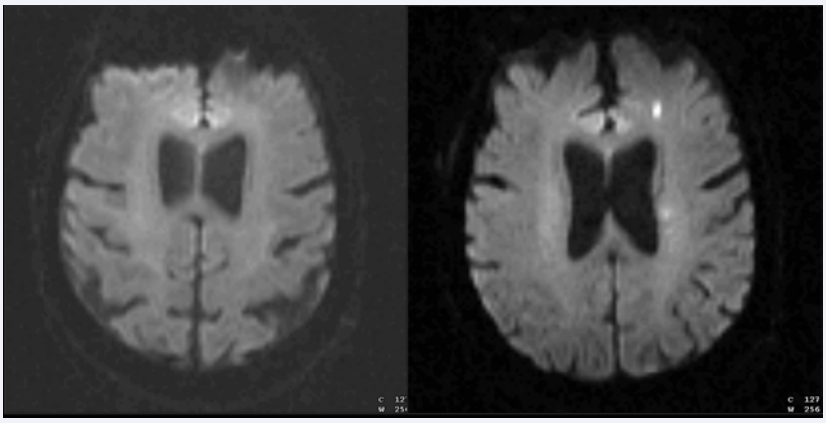

Figure 2 Diffusion Imaging Pre- and Post-surgery.
2D clinical diffusion-weighted images from 86 year old male who underwent total knee arthroplasty. Images are pre- and post-surgery, respectively. Presurgery MRI was acquired 24 hours before surgery. Post-surgery image was acquired within 48 hours of surgery. Very bright signal in the left frontal lobe of the post-surgery image indicates a new stroke.

disease manifesting as white matter hyperintensities or small cortical to subcortical infarctions by increasing the conspicuity of associated gliosis which assumes a bright signal on this type of images [24]. FLAIR images are thus important for assessing cerebrovascular disease, with greater amounts being associated with worse executive function following surgery [14,17,18]. Diffusion weighted imaging (DWI) has been developed for detection of areas of acute to early subacute infarctions. DWI is based on the random (Brownian) motion of water through tissues (referred to as diffusion). Diffusion can range from freely mobile to restricted. Acute infarction is the best-known disease process to cause restricted motion of water. During an acute infarction, the interruption of cerebral blood flow leads to rapid breakdown of the cellular energy metabolism and dysfunction of ion exchange pumps, resulting in a massive shift of water from the extracellular to the intracellular space. The water thus gets 'trapped' within the cells and results in restricted diffusion that manifests as very bright signal on DWI. DWI has high sensitivity for detecting acute to early subacute infarctions (Figure 2) and for differentiating them from areas of chronic ischemic changes [25]. This sequence does, however, have suboptimal specificity because other disease processes, such as infections or certain neoplastic lesions, can also display restricted diffusion. Acute to subacute blood products may mimic areas of restricted diffusion as well. This may pose a diagnostic dilemma in post-surgical patients as blood products within a cavity can demonstrate restricted diffusion and mimic an abscess. A similar problem can occur with an intraparenchymal hemorrhage. In this instance, it might be difficult to determine if the signal abnormality is related to a hemorrhagic infarction, an underlying hemorrhagic metastasis or a simple hemorrhage. Continuous follow-up or detection of an additional non-hemorrhagic lesion(s) on MRI will assist in the correct diagnosis. In spite of its limitations, DWI is an important tool for use in situations where stroke is a concern, such as in older adults perioperatively. In particular, silent strokes might escape a correct clinical diagnosis and contribute to the development of POCD.

Imaging logistics

2D versus 3D acquisitions: Many clinical scans are acquired

as 2-dimensional (2D) data sets in one or more of the three major planes – axial, sagittal, or coronal. While in-plane resolution can be high and image quality good, 2D scans provide limited ability for multiplanar reformations, as each slice is usually three or more millimeters in thickness. In contrast, 3D sequences consist of continuous thin section images (≤ 1mm) making reformations in any desirable plane possible, particularly when acquired as isovoxel (each voxel is a cube). This comes at the expense of significantly increased acquisition time (in general at least double the time to the equivalent 2 D technique). Therefore, 3D images are predisposed for motion degradation. Nevertheless, 3D acquisitions are essential for certain clinical situations such as stereotactic guidance of biopsies or hippocampal volume measurements in seizure patients. These are also recommended for research purposes as they facilitate quantitative analysis such as volumetric assessment of specific brain areas for atrophy or determination of white matter disease burden. In both settings, the added acquisition time, that is even longer for advanced 3D sequences (see below), needs to be balanced against the specific needs of a patient and patient's ability to hold still and the risk of acquisition of non-useable data sets because of motion degradation.

Acquisition time: Each standard 2D MRI sequence requires 3 to 6 minutes of scanning time for every plane (coronal, axial, sagittal), although shorter protocols are available with uncooperative patients at the expense of image quality. A standard brain MRI without gadolinium (a MRI contrast-enhancement agent) is usually composed of at least 5 sequences (sagittal T1, axial FLAIR, T1, T2, and DWI), resulting in an acquisition time of about 20 minutes. Addition of post-gadolinium images typically increases the scanning time by about 10 minutes if post-contrast T1-weighted images are acquired in axial and coronal planes. In general, MRI examinations lasting longer than 45 minutes are not well tolerated by patients. Therefore, careful protocolling of each MRI examination by the radiologist is required with preferential performance of critical sequences and imaging planes at the beginning of the study to minimize the risk of suboptimal image quality secondary to motion degradation or deliverance of an incomplete study. For example, in an acute stroke patient the DWI is most critical to detect an acute or early subacute infarction and should be performed first. Such an approach is also recommended for researchers, although motivated research participants can usually tolerate longer examinations lasting up to 75 minutes with minimal discomfort and movement.

ADVANCED SEQUENCES FOR RESEARCH APPLICATIONS

Structural – advanced applications. With high quality 3D protocols, accurate quantification of brain, specifica anatomical regions, and brain pathology is possible. Using research tools such as Freesurfer [21] or FDA-approved clinical tools (e.g., NeuroQuant: http://www.cortechslabs.com; [26]), it is possible to quickly acquire static or longitudinal measures of atrophy or brain pathology. Such volumetric MRI methods are being applied to preoperative MRIs in order to better predict POCD [14] as well as post-operatively to assess possible brain damage related to the surgical intervention.

Structural and functional advanced applications

Diffusion tensor imaging (DTI) is a noninvasive method that allows the mapping of the diffusivity of molecules, water in particular, in the brain tissues. A primary reason for measuring diffusion of water in the brain is to investigate diffusion along white matter tracts; this directional (anisotropic) diffusion reflects the integrity of connectivity of brain. During acquisition of DTI, gradients are applied in many different directions to allow the detection of diffusivity within tissues. The strength and the width of these gradients as well as the time between each of the gradients determines the 'diffusion weighting' of the pulse, also called the 'b value'. Low b values result in low diffusivity and resemble T2 images. DTI requires a b value of at least 800 to provide sufficient representation of diffusivity in tissue for clinical and research applications. However, b values of 3000 or greater and acquisition of at least 45 directions is necessary for optimal diffusion data quality for research investigations [27]. Acquiring DTI data at sufficient spatial resolution requires considerable time with acquisition times as high as 35 minutes or more, depending on the number of directions acquired, image resolution, and the b value. At a minimum, 6 directions are needed to reconstruct basic research DTI metrics, such as fractional anisotropy (FA) and mean diffusivity (MD), however higher quality of data are required for detection of more subtle brain changes. DTI metrics are useful and have been shown to be predictive of various cognitive difficulties in older adults [28,29].

High angular resolution diffusion imaging (HARDI) is a mathematical model based on the DTI technology that allows assessment of more complex representations of tissue, in particular of crossing fibers that cannot be separated by a simple DTI analysis. HARDI methods allow researchers to model white matter fiber pathways with excellent histological validity. Models of fibers are used clinically with surgical planning (such as for deep brain stimulator implantation [30,31]; tumor resection [32]) as well as in numerous research populations. While applications to POCD are limited thus far, this is an area of growing interest. In addition to visualizing pathways, structural 'connectivity' between brain regions can be quantified [33] and then those values can be correlated with cognitive or behavioral variables.

Functional MRI is based on calculating blood oxygen level-dependent (BOLD) signal fluctuations. These changes can be measured in the 'resting' brain or in response to stimuli as part of a task. Resting state fMRI (RS-fMRI) is thought to reveal natural patterns of brain activity when individuals are at rest. Numerous networks of functionally connected regions (measured through 'functional connectivity') have been identified, with the default mode network (DMN) the most studied. This network is thought to be active when individuals are at rest; the DMN shows decreased activity during cognitive tasks. Functional connectivity of the DMN and memory-supporting brain regions are reduced in Alzheimer's disease and mild cognitive impairment, with neuroimaging able to accurately distinguish demented from non-demented patients [34]. Resting state fMRI is being applied to many other clinical populations, including those undergoing tumor resection, epilepsy surgery, patients with major depressive disorder, and those with ADHD (for a review see [34]). Further, there are suggestions of reductions in brain

functional connectivity following total knee arthroplasty [35]. While RS-fMRI is still a research protocol, it is possible to acquire within the context of a clinical scan, although motion during the scan (an issue in older and inpatient populations) can result in spurious statistical findings [36]. Work is continuing to establish the clinical utility of RS-fMRI and regularly acquiring research-quality data in clinical settings will greatly benefit this process of validation.

DISCUSSION AND CONCLUSION

POCD in older adults is an area of significant concern to clinicians and researchers. Advancing the clinical science of POCD will require integrated, multidisciplinary teams. Regularly acquiring advanced clinically-relevant MRI data as well as developing clinical imaging analysis tools will be necessary for understanding the etiology of POCD and better predicting and managing patients' outcomes, which in turn will improve patients' care.

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