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Brain Shift in Neuronavigation of brain tumours: A Review

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Conflict of Interest
All authors declare they have no conflict of interest.

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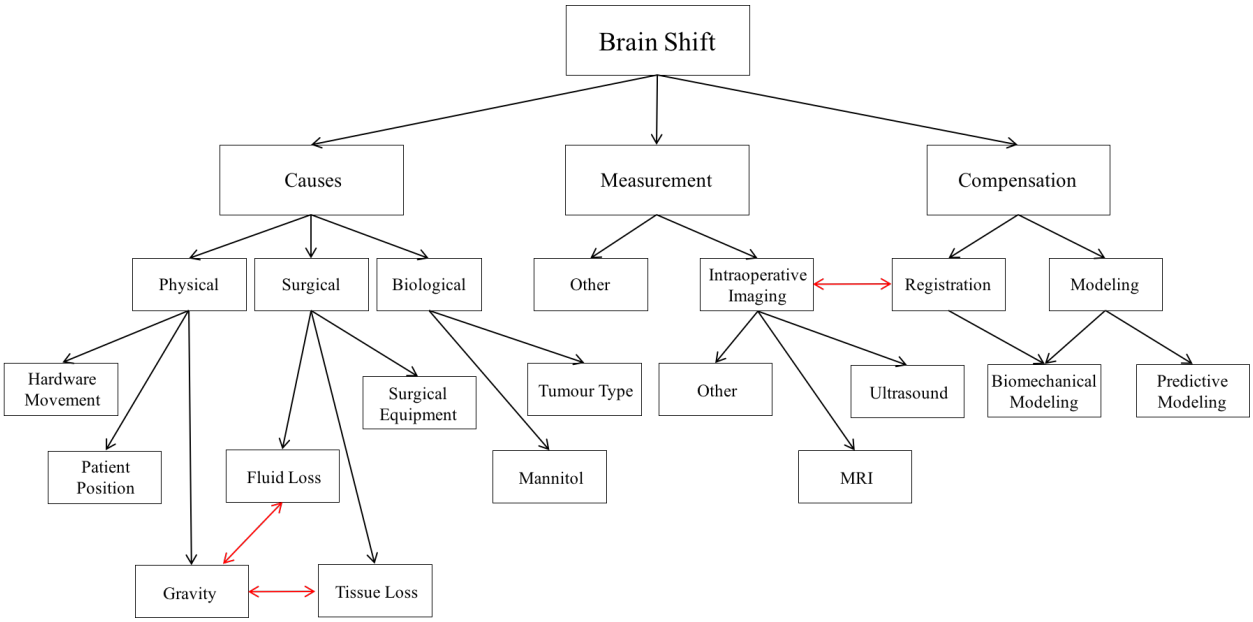
ABSTRACT

Purpose: Neuronavigation based on preoperative imaging data is a ubiquitous tool for image guidance in neurosurgery. However, it is rendered unreliable when brain shift invalidates the patient-to-image registration. Many investigators have tried to explain, quantify, and compensate for this phenomenon to allow extended use of neuronavigation systems for the duration of surgery. The purpose of this paper is to present an overview of the work that has been done investigating brain shift.
Methods: A review of the literature dealing with the explanation, quantification and compensation of brain shift is presented. The review is based on a systematic search using relevant keywords and phrases in PubMed. The review is organized based on a developed taxonomy that classifies brain shift as occurring due to physical, surgical or biological factors.
Results: This paper gives an overview of the work investigating, quantifying, and compensating for brain shift in neuronavigation while describing the successes, setbacks, and additional needs in the field. An analysis of the literature demonstrates a high variability in the methods used to quantify brain shift as well as a wide range in the measured magnitude of the brain shift, depending on the specifics of the intervention. The analysis indicates the need for additional research to be done in quantifying independent effects of brain shift in order for some of the state of the art compensation methods to become useful.
Conclusion: This review allows for a thorough understanding of the work investigating brain shift and introduces the needs for future avenues of investigation of the phenomenon.

GRAPHICAL ABSTRACT



KEYWORDS

Brain shift; Image guided neurosurgery; neuronavigation; Registration Errors; Intraoperative imaging

INTRODUCTION

Since the introduction of the first intraoperative frameless stereotactic navigation device by Roberts *et al.* in 1986 (Roberts et al. 1986), image guided neurosurgery (IGNS), or "neuronavigation" has become an essential tool for many neurosurgical procedures due to its ability to minimize surgical trauma by enabling precise localization of surgical targets. Over the past 30 years, the growth of this technology has enabled application to increasingly complicated interventions including the surgical treatment of malignant tumours (Muacevic et al. 2000; Willems et al. 2006; Benveniste and Germano 2005; Du, Zhou, and Mao 2003; Ozawa et al. 2009; Roberts et al. 1986; Carvi and Hollerhage 2007; Coenen et al. 2001; Idris et al. 2011; Jung et al. 2006; Suess et al. 2007; Tuominen et al. 2003; Unsgaard et al. 2002; Wong, Poon, and Lam 2001; Yamada et al. 2010; Reinges et al. 2004; Gerard et al. 2016), neurovascular disorders (Akdemir et al. 2007; Kersten-Oertel et al. 2015; Kim et al. 2007; Marinho et al. 2012; Mathiesen et al. 2007; Rivero-Garvia et al. 2009; Tanei et al. 2010; Walkden et al. 2015), epilepsy (Chamoun, Nayar, and Yoshor 2008; Cui et al. 2014; Eross 2011; Eross et al. 2009; Holowka et al. 2004), and deep brain stimulation (DBS) (Beriault et al. 2011; Beriault et al. 2014; Beriault et al. 2012; Pallavaram et al. 2010). Image guidance systems provide a surgeon with the tools necessary to better visualize and interpret patient-specific volumes of anatomical, vascular and functional data while also being able to understand some of their inter relationships. For example, a surgical target and the surrounding soft tissue anatomy can be viewed in exquisite detail with magnetic resonance imaging (MRI), eloquent cortex that must remain intact can be mapped out with positron emission tomography (PET) and functional MRI (fMRI), while digital subtraction angiograms (DSA) and diffusion tensor imaging (DTI) can be used to visualize a vessel-free path that minimizes damage to white matter fiber tracks. The integration of this information into a comprehensive patient-specific model enables surgeons to preoperatively evaluate the risks involved and define the most appropriate surgical strategy. Perhaps more importantly, such systems enable surgery of previously inoperable cases given the potential identification of surgical corridors through IGNS-identified non-critical areas. For intraoperative use, neuronavigation systems must relate the physical location of a patient with the preoperative models by means of a transformation that relates the two paradigms through a patient-to-image mapping. By tracking the patient and a set of specialized surgical tools, this mapping allows a surgeon to point to a specific location on the patient and see the corresponding anatomy in the previously acquired preoperative images.

Unfortunately, brain movement during surgery invalidates the patient-to-image mapping and thus reduces the effectiveness of using preoperative images for intraoperative surgical guidance. Brain shift is a complex spatio-temporal phenomenon with a wide variety of causes related to physiological, chemical, and physical factors that cannot be properly accounted for with neuronavigation systems based solely on preoperative images. As a result, most surgeons use IGNS systems to approach a surgical target but justifiably no longer trust the system throughout the entirety of an operation. There has been extensive research performed over the last 20 years that has focused on characterizing and correcting for the brain shift phenomenon. The main goal

of this review is to provide a comprehensive analysis of the current understanding of the underlying technical, surgical and biological factors of this phenomenon, as well as the methods that have been developed to correct for it in the context of improved accuracy for neuronavigation.

Workflow of Neuronavigation Systems

The main components of a traditional neuronavigation system consist of a tracking device that tracks the position of the patient and surgical tools, a computer console and display that displays images and other navigation information, and finally accessories such as navigation probes and reference frames. In addition to these tools, the surgical microscope has become a common presence in the operating room and its use during surgery is discussed in McInerey 2000 (McInerey and Roberts 2000). The workflow of neuronavigation systems for intraoperative guidance is shown in Figure 1 and can be separated into 4 steps.

1. Image scanning – the patient is scanned to acquire necessary images for navigation.
2. Surgical planning – the preoperative images are imported into the neuronavigation system, co-registered together and then used for planning.
3. Patient-to-Image registration – The mapping between the physical space of the patient and the virtual space of the images is determined by either homologous landmark (or fiducial) matching or surface matching.
4. Intraoperative navigation – Using the transformation determined in the previous step, a tracked tool can be placed in the physical space of the patient and the corresponding anatomical location can be shown in the virtual space, i.e. on the images.

A major limitation of traditional neuronavigation systems based on preoperative imaging is the loss of accuracy in the mapping determined at step 3 that leads to a physical location on the patient being incorrectly reported in relation to the images used for guidance. These spatial errors arise from the violation of two basic assumptions:

(1) That the equipment, registration and images are perfectly accurate. This assumes that the tracking device and associated hardware are free of positioning error, the registration between the patient and image spaces is free of errors and all preoperative images are free from any geometrical distortions.
(2) That the equipment and volume of interest form a rigid system. This assumes that structures of interest within the brain remain in the same position as when they were imaged, with respect to both the external features used to determine the patient-to-image mapping as well as the tracking device throughout the procedure.

Most of the features of assumption (1) are usually described as technical inaccuracies and vary between the systems being used for guidance. This also assumes that the contrast-enhanced images of lesions shown within images delineate all of the disease pathology, however this is often untrue given the technical limitations of the current standard-of-care imaging. In assumption (2) are commonly grouped as inaccuracies related to the phenomenon of brain shift. Most commercially available tracking devices can provide position and orientation information with sub-millimeter accuracy. Many authors have spent time characterizing different tracking systems used for IGNS. The interested reader is directed to Khadem 2000 (Khadem et al. 2000)

and Gerard 2015 (Gerard and Collins 2015) for a description of errors related to optical tracking systems, Hummel 2005 (Hummel et al. 2005) and Yaniv 2009 (Yaniv et al. 2009) for a description of errors related to electromagnetic tracking systems, and finally Manor 1993 (Manor et al. 1993) and Cinthio 2005 (Cinthio et al. 2005) for a description of errors related to ultrasonic tracking systems. The main conclusion of these studies is that errors related to tracking of tools and patients have an inverse relationship with distance. As the tools being tracked move further from the tracking source the potential for errors increase. In addition, as the distance between tracked tool and reference gets increasingly large, the potential for errors associated with the system are amplified. Consequently, the design of the tools themselves has been studied in regards to minimizing these errors (West et al. 2004) and is an important aspect of neuronavigation hardware design.

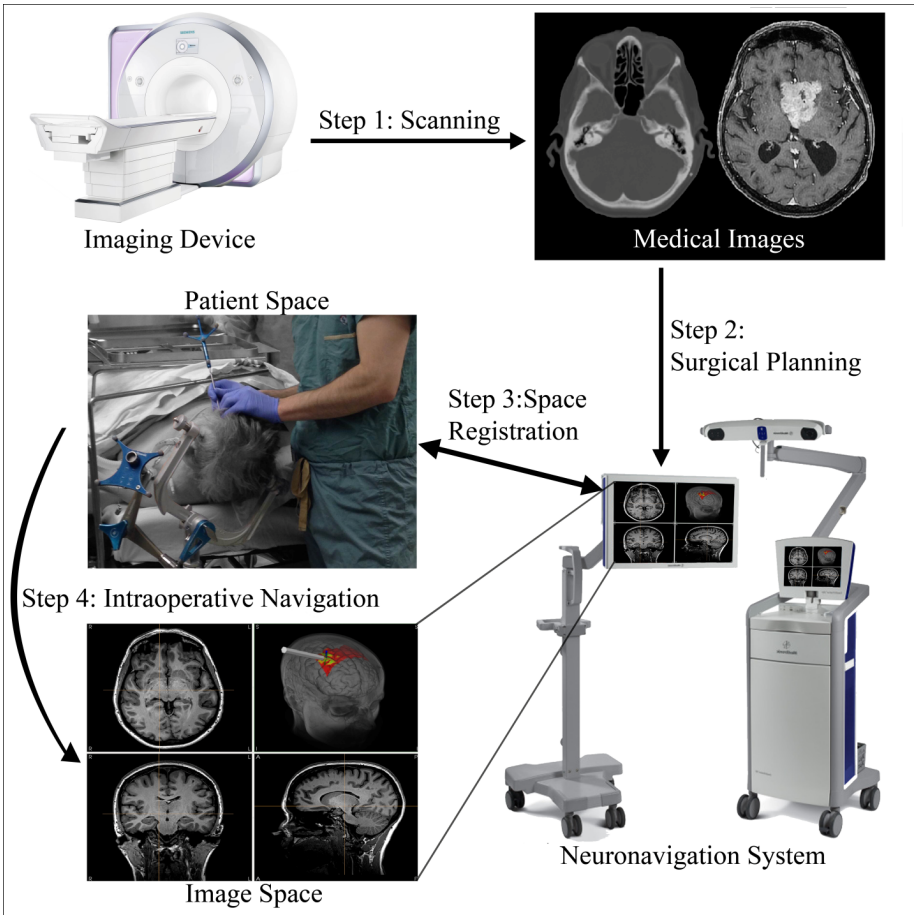


Figure 1: Workflow of traditional neuronavigation. In Step 1 the patient is scanned to acquire medical images. In Step 2 these images are imported into a neuronavigation system for surgical planning. In Step 3 the patient-to-image mapping is determined allowing for Step 4, intraoperative navigation.

Another important contributor of technical inaccuracies arises from the distortions in the preoperative images of a patient, specifically in MRI images, that lead to a difference between the anatomy of a patient in the physical and virtual spaces (Maurer et al. 1996). A main cause of these distortions is inhomogeneities of the magnetic field (Jezzard and Clare 1999). Hutton *et al* showed that inhomogeneities in the magnetic field caused by magnetic susceptibility differences

at an air-tissue interface can result in noticeable distortions in the inferior temporal and frontal lobes (Hutton et al. 2002). Many authors have taken approaches to correct for these distortions (Cusack, Brett, and Osswald 2003; Zeng and Constable 2002; Li et al. 2008; Dragonu et al. 2009; Andersson and Skare 2002; Hunsche et al. 2004). Another important feature related to preoperative imaging is the voxel size used during acquisition. In most clinical interventions, an imaging matrix such as a 512 x 512 is used that results in a pixel size of 0.5 mm. While the contribution of this factor towards overall accuracy is generally smaller than other factors that are encountered, it is important to monitor when lower quality images are used (Gerard and Collins 2015).

The largest source of error contributing to assumption (1) comes from determining the transformation between the physical and virtual image spaces. Many different strategies for determining this mapping have been reported in the literature, including surface based registration (Ryan et al. 1996; Raabe et al. 2002; Marmulla et al. 2004; Stieglitz et al. 2013; Woerdeman et al. 2007; Thompson et al. 2011; Mascott et al. 2006; Paraskevopoulos et al. 2010) or homologous paired point matching of landmarks, fiducials, and/or screws (Watanabe et al. 1991; Laborde et al. 1992; Golfinos et al. 1995; Sipos et al. 1996; Hassfeld et al. 1997; Helm and Eckel 1998; Brinker et al. 1998; Germano et al. 1999; Villalobos and Germano 1999; Gumprecht, Widenka, and Lumenta 1999; Wolfsberger et al. 2002; Woerdeman et al. 2007; Pillai, Sammet, and Ammirati 2008; Pfisterer et al. 2008; Thompson et al. 2011; Mercier et al. 2011; Mascott et al. 2006; Kall et al. 1996; Smith, Frank, and Bucholz 1994; Maurer et al. 1997; Paraskevopoulos et al. 2010; Gerard et al. 2015). In addition to these extra-cranial methods, several authors have attempted to perform the initial patient-to-image registration once the cortical surface has been exposed (Cao et al. 2008; Nakajima et al. 1997) using laser range scanners and vessel registration techniques. The accuracy of these methods varies largely between different systems and techniques used. A comprehensive description of the reported accuracies is shown in Table 1[1].

The importance and relevance of these reported accuracies is two fold: 1) there is a relatively large range of acceptable accuracies with different neuronavigation systems depending on the type of registration procedure, imaging and system used, and 2) this represents the initial accuracy of the image guidance procedure before any surgical intervention has begun. The implications of 2) are often underestimated. Since these registration procedures are based on external features of the patient, the inaccuracies present will also be propagated and potentially amplified into the surgical region of interest. This will have an indirect effect on the perceived brain shift since the initial mapping is already imperfectly representing the location of preoperatively imaged anatomy relative to the physical location of the anatomy. When considering the effects of brain shift this is an important starting point in trying to differentiate whether the shift comes from actual biological phenomena or from physical shortcomings. Many authors have reported subsequent brain shifts after this initial misregistration and have used different methods to try and improve on this source of error but the reports are commonly highly variable between studies and techniques and lack a common standardized approach for sharing results. With this review we intend to assemble the literature focused on describing, measuring

[1] Table 1 is an expanded and updated list of references and associated registration errors as that presented by Stieglitz et al. 2013.

and quantifying brain shift in order to see the state of the art in the field as well as what is required for the future.

Table 1: Reported accuracy for patient-to-image registration in the literature using varying techniques and systems

Reference	Navigation System	Paired Point Matching (mm)			Surface Matching (mm)		
		Landmarks	Fiducials	Screws	Pointer	Laser	Other
Watanabe 1991 (Watanabe et al. 1991)	Neuronavigator		2.5				
Laborde 1992 (Laborde et al. 1992)	CA Localizer		3				
Smith 1994 (Smith, Frank, and Bucholz 1994)	NeuroStation		< 2				
Golfinos 1995 (Golfinos et al. 1995)	FARO Surgicom	5.6 (CT)	2.8 (CT)				
		6.2 (MRI)	2.8 (CT)				
Sipos 1996 (Sipos et al. 1996)	FARO Surgicom	3.1 (CT)	2.3 (CT)				
		2.7 (MRI)	2.8 (MRI)				
Ryan 1996 (Ryan et al. 1996)	Flashpoint 3D digitizer and Sparcstation2						4.8 ± 3.5
Kall 1996 (Kall et al. 1996)			< 2				
Maurer 1997 (Maurer et al. 1997)	ACUSTAR I		1.00 ± 0.52 (CT)				
			1.28 ± 0.64 (MRI)				
Nakajima 1997 (Nakajima et al. 1997)	Unspecified	1.3 ± 1.4 (vessel-to-vessel)					
Helm 1998 (Helm and Eckel 1998)	FARO Surgicom		2.1				
Brinker 1998 (Brinker et al. 1998)	Zeiss MKM			0.7 ± 0.2			
Germano 1999 (Germano et al. 1999)	OD System	3.4 ± 0.2	1.7 ± 0.2 (preop)				
			2 ± 0.2 (postop)				
Villalobos 1999 (Villalobos and Germano 1999)	OD System	3.4 ± 0.4	1.6 ± 0.1				
Gumprecht 1999 (Gumprecht, Widenka, and Lumenta 1999)	BrainLab VectorVision		4 ± 1.4				
Raabe 2002 (Raabe et al. 2002)	BrainLab VectorVision2					1.8 ± 0.8 (frontal)	
						2.8 ± 2.1 (occipital)	
Wolfsberger 2002	EasyGuide	3.2 ± 1.0	2.9 ± 1.0				

(Wolfsberger et al. 2002)	(Philips)					
Marmulla 2004 (Marmulla et al. 2004)	SSN++					1.2 ± 0.3
Woerdeman 2007 (Woerdeman et al. 2007)	StealthStation TREON Plus	4.0 ± 2.1 (frontal CT)	2.5 ± 1.1 (frontal CT)		4.8 ± 2.2 (frontal CT)	
		4.0 ± 2.0 (frontal MRI)	1.9 ± 0.8 (frontal MRI)		4.0 ± 2.0 (frontal MRI)	
		6.0 ± 2.7 (nonfrontal CT)	3.2 ± 1.1 (nonfrontal CT)		6.0 ± 2.7 (nonfrontal CT)	
		5.6 ± 1.8 (nonfrontal MRI)	2.3 ± 1.0 (nonfrontal MRI)		5.5 ± 1.8 (nonfrontal MRI)	
Pillai 2008 (Pillai, Sammet, and Ammirati 2008)	Stryker Navigation System			0.91 ± 0.28		
Pfisterer 2008 (Pfisterer et al. 2008)	StealthStation	4.0 ± 1.7	3.5 ± 1.1		3.3 ± 1.7	
Cao 2008 (Cao et al. 2008)	StealthStation	1.6 ± 0.5 (skin)				
					1.7 ± 0.5 (Vessel – MR)	
					3.9 ± 3.4 (unconstrained intensity)	
					2.0 ± 0.9 (constrained intensity)	
Thompson 2011 (Thompson et al. 2011)	Stealth Station	1.9 0.5	1.3 0.5			
Mercier 2011 (Mercier et al. 2011)	IBIS Neuronav	4.9				
Steiglitz 2013 (Stieglitz et al. 2013)	StealthStation					2.9 ± 3.3
Mascott 2006 (Mascott et al. 2006)	StealthStation	4.8 ± 1.9	3.7 ± 1.8	1.7 ± 0.7	4.2 ± 1.6	
Paraskevopoulous 2010 (Paraskevopoulos et al. 2010)	BrainLAB VectorVision				2.61 ± 1.56	
	Stryker Leibinger				2.51 ± 1.49	
Gerard 2015 (Gerard et al. 2015)	IBIS Neuronav	3.5 ± 1.8 (8 landmarks) 5.5 ± 2.5 (9 landmarks)				

METHODS

Search Methodology

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines without prior publication of the review protocol (Moher et al. 2009). PubMed[2] was used to search several specific keywords and phrases:

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(brain or tissue) and (shift or deformation) or (modeling or predicti* or
registration) or (measure* or quantif*) or (intraoperative or imag*) or
(9euronavigation accuracy)
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All returned titles were screened and any non-English, duplicate or clearly irrelevant entries were excluded. In addition to the PubMed results, we included appropriate references of the first set of selected publications as well as some handpicked references that did not meet the search criteria but were relevant to the review. All of the reviewed articles were published between 1997 and 2015 with exception of Kelly 1986 (Kelly et al. 1986) which is the first report on brain shift in a peer-reviewed journal and was included for historical completeness. In order to achieve an overview of how the understanding of factors related to brain shift have evolved, as well as the methods that have been developed to compensate for it, we concentrated on publications that focused on either the measurement and description of the phenomenon or on methods to compensate for the phenomenon. The first inclusion criteria used during the selection process was that the work had to be focused on brain shift in the paradigm of IGNS. Imaging studies were only included if the work was on clinical data and the focus of the imaging was to measure brain shift. Imaging studies also had to focus on brain shift in cerebral tumours. Furthermore, for publications that were more mathematical in nature and focused on compensation of brain shift, validation of the compensation method on either clinical or phantom had to be included or provided. For articles that focused on the methodology of brain shift compensation, if work from a specific research group or project had been published more than once and without significant modifications, only the most recent publication was reviewed. Case studies are not included in this review. From an initial 1993 articles, 45 papers were identified as duplicates and 8 non-English papers were removed. 1559 papers were excluded for lack of relevance for the review based on evaluation of the title and abstract. From the 389 remaining papers, 238 met exclusion criteria or failed to meet inclusion criteria. Twenty-three papers were excluded, as they reported on a previously reported project. A total of 128 publications remained for review. A four-phase flow diagram (Moher et al. 2009) is presented in Figure 2 showing the search strategy and inclusion and exclusion criteria.

[2] http://www.ncbi.nlm.nih.gov/pubmed/

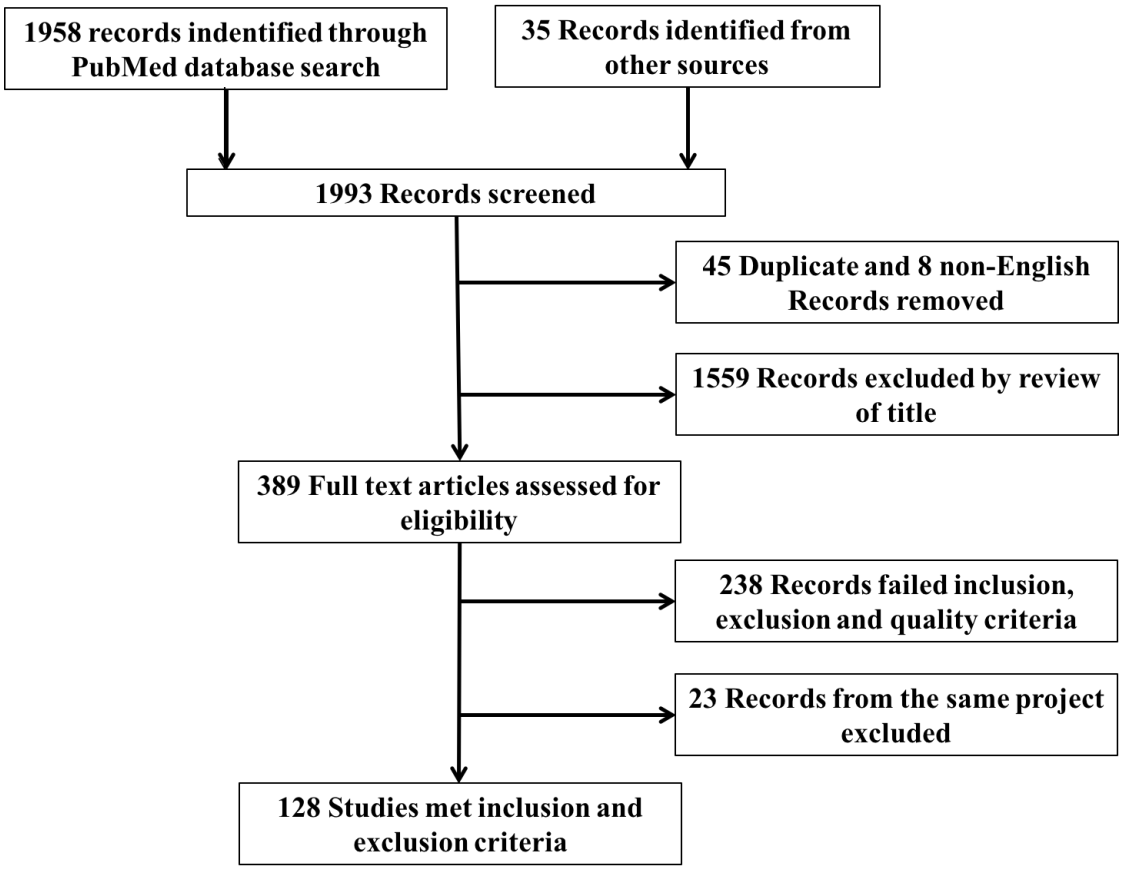

Figure 2: Screening and selection process for studies included in the review

Brain Shift Taxonomy

In order to assist with the clarity of the review and the discussions to follow we propose a model to describe the different aspects related to brain shift (c.f., Fig. 3). To begin we define brain shift in the following way – *any factor, physical, surgical, or biological, that violates the rigid body assumption of 10euronavigation creating a difference between the reported location of anatomy in the virtual image and patient spaces*. We separate the discussion of brain shift into three categories, 1) factors that cause brain shift, 2) methods for quantifying brain shift, and 3) methods that have been developed to correct for brain shift. The first component, causes of brain shift, is separated into three categories; i) physical, ii) surgical, and iii) biological. The second component, quantifying brain shift, is separated into two categories; i) intraoperative imaging – the most popular method – and ii) "other" which, as the name suggests, are all other methods of quantification. The third component, compensation of brain shift, is separated into two categories; i) registration methods, which generally focus on relating preoperative and intraoperative imaging, and ii) modeling, which is focused on the mathematical and statistical principles of predicting brain shift in order to compensate for it without the need for intraoperative imaging. In the following subsections we will go into detail of each part of the diagram.

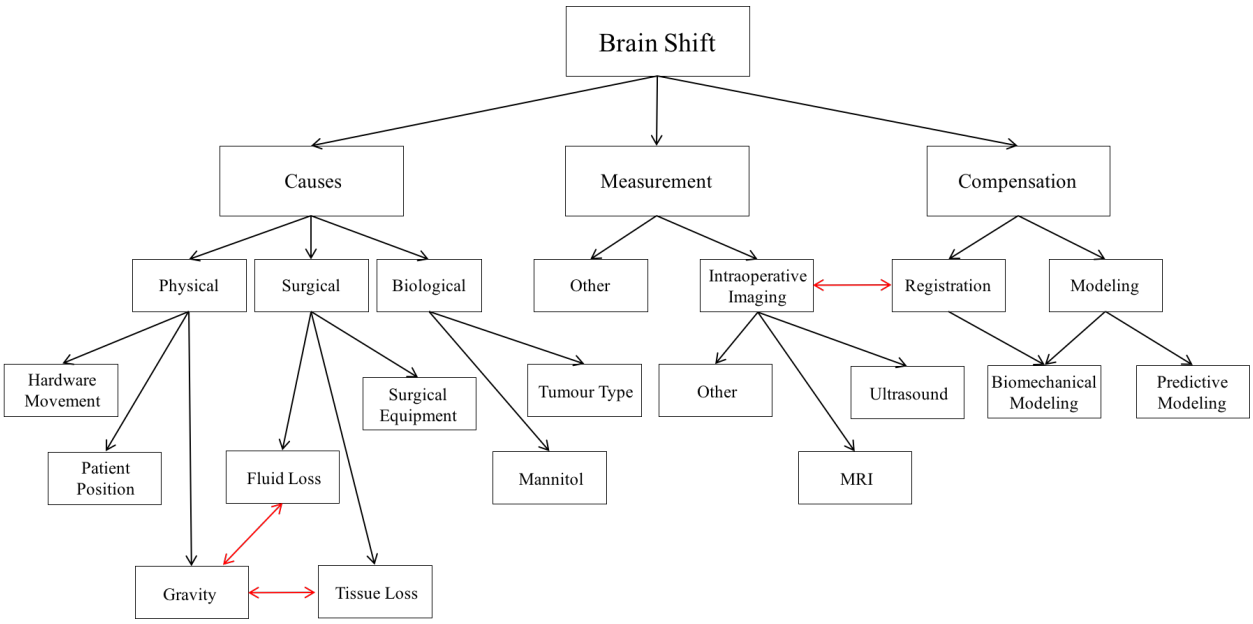

Figure 3: Overview of brain shift and the relationships to its causes, measurement techniques, and compensation methods.

CAUSES OF BRAIN SHIFT

The first article to report on the phenomenon of brain shift was published in 1986 by Kelly *et al.* (Kelly et al. 1986), just prior to the release of the first frameless stereotaxic system developed by Roberts *et al.* (Roberts et al. 1986). Kelly *et al.* (Kelly et al. 1986) observed a *dislocation* of small steel balls placed along the line of view of the surgeon during volumetric stereotaxy. While they documented observing the shift, at that time there was no equipment available to perform any extensive quantitative measurements of the phenomenon. In this section we aim to discuss the work that has been done to describe the different causes of brain shift. We classify based on our taxonomy thereby separating the causal factors into physical, surgical, or biological categories. Physical factors are those that relate directly to the 11euronavigation system hardware, the patient's position during preoperative imaging and during the surgery as well as the effects of gravity. Surgical factors are those that relate to the use of different surgical equipment, such as retractors, as well as fluid and tissue loss throughout the surgery. Biological factors encompass details related to the tumour type and location as well as the use of different drugs to manage intracranial pressure during surgery (e.g., Mannitol).

Neuronavigation Hardware Movement

We open the discussion of brain shift with work investigating a physical factor that is external to the patient's head but can have a significant effect on the rigid body assumption that invalidates the accurate representation of the patient's physical location in the virtual images. As can be seen in Figure 1, a patient undergoing IGNS has their head immobilized through the use of a head clamp such as the Mayfield clamp® (Mayfield Clinic, Cincinatti, Ohio USA). In 11euronavigation, the purpose of this clamp is to ensure the position of the patient's head is constant relative to the tracked reference frame that is attached to the clamp. Several factors lead to a change in position of either the patient's head or the reference frame throughout a procedure. First, the registration procedure for determining the patient-to-image mapping is done prior to

sterilization of the surgical environment and thus the reference frame is either removed and replaced with a sterile one or in some situations simply covered with a sterile drape. Since the patient-to-image mapping previously determined is related to the exact position of the reference frame, any displacement of the replaced reference frame will lead to a shift in the displayed preoperative images (Stieglitz et al. 2013). One of the most important technical factors relates to the movement of the patient's head relative to the clamp. The Mayfield head clamp was invented in 1974, many years before frameless stereotaxy, and despite its success, it was not intended to support frameless navigation and allows for minor head movement that can lead to a considerable mismatch between the patient and images in situations where large forces are applied (e.g. using a hand drill to create burr holes). Inaccuracies due to this kind of movement have been described by Ganslandt (Ganslandt et al. 2002), Woerdeman (Woerdeman et al. 2007) and more recently by Stieglitz (Stieglitz et al. 2013). Systems using infrared tracking, which encompass a 3-dimensional stereo camera and passive marker spheres for image-patient coupling, can have artifacts caused by inhomogeneous reflection of the infrared light flashes. Such effects have been investigated in Muacevic (Muacevic et al. 2000), Khadem (Khadem et al. 2000), Stieglitz (Stieglitz et al. 2013) and Gerard (Gerard and Collins 2015).

Patient Positioning

The issue of patient positioning is an important factor in IGNS. Difference in patient positioning between preoperative imaging acquisition and in the operating room can lead to significant differences between the virtual and physical representation of anatomy (Wang and Song 2011; Benveniste and Germano 2005). With the exception of posterior fossa and some occipital lobe based procedures, the most common positioning of a patient intraoperatively is supine with a rotation of the head that will allow for the lobe of surgical interest to be exposed and minimum fluid leakage. In contrast, preoperative imaging can be performed in either a supine or prone position, depending on the type of radiofrequency coil being used and the imaging protocol being performed. The effect of patient positioning and changes in the anatomical position of brain structures has only been sparsely evaluated in the literature. Schnaudigel (Schnaudigel et al. 2010) reported deformations in the lateral direction of up to 1.7 mm around central brain structures depending on the patient's position in an MR scanner. This study highlights the importance of imaging position on accurate navigation and furthermore, demonstrates that this is a non-trivial factor when trying to maximize accuracy. It is not clear whether this is related to head-position dependent brain shift or geometric distortion in the MRI scanner and more studies are needed to quantify the effects of brain shift with different head positions.

Gravity

One of the largest physical factors that contribute to brain shift is the effect of gravity. The forces of gravity are an important consideration during patient head positioning; the head must be positioned to minimize loss of cerebrospinal fluid (CSF) and blood as well as minimize tissue sag due to gravitational forces on the brain. Early investigations of brain shift suggested that the primary cause was gravity and it was measured as sagging of the brain due to tissue removal. The largest effect of gravity is seen when resection of tumours is performed and healthy tissue above a lesion becomes unsupported. This causes local sagging of the undercut brain tissue that is difficult to model due to its highly nonlinear nature (Nabavi et al. 2001).

Surgical Equipment

The category of surgical equipment is a relatively vague and a difficult effect to quantify since any interaction from the surgical staff that inadvertently changes the patient's position relative to the reference will cause a discrepancy between reported location of anatomy in the physical and image spaces. However, there have been several reports of certain equipment used during a surgical intervention that have a more prominent effect. Stieglitz 2013 (Stieglitz et al. 2013) reported on the significant effect that both skin retractors and surgical drapes have in invalidating the initial patient-to-image mapping. Skin retractors are used in many surgical cases to improve exposure of the bone for a craniotomy as well as to keep the skin flap out of the surgical work environment. The application of a single retractor applies a lateral force of approximately 10–15 N. In the case of 3 retractors, a common scenario, this would result in a force of 30 N – 45 N, this can easily translate into a movement of the head of several mm relative to the external reference. In addition, the length of the surgery, and thus the length of time that the retractors remain pulling on the skin, can have a compounded effect, degrading accuracy over time. Surgical drapes are typically placed around the surgical field to maintain a clean and sterile environment. The drapes are attached to different parts of the patient as well as to the Mayfield clamp®. The attachment of these drapes, however, can have a considerable effect on accuracy for a variety of reasons. As surgery progresses, the drapes can become soaked with blood, irrigation, or CSF increasing their weight and thus putting a downward force on the applied location. In addition, the drapes are generally connected to different portions of the surgical field including the Mayfield clamp, patient's head, surgical table and other instruments in the OR. While attaching the drapes, it isn't uncommon to pull and straighten them with significant force to achieve a smooth and sterile field, this enhances the force applied on the patient and clamp and can cause additional movement relative to the reference frame (Wang and Song 2011). Another important surgical factor to consider is the method that is used to make the craniotomy. In many cases, an electric drill facilitates the procedure allowing for short duration and minimal amount of applied force. Sometimes it is not feasible to use an electric drill, especially for cases where the patient is awake or there are other underlying causes that prevent their use, thus a manual burr hole drill and a manual saw may be used (Coenen et al. 2011). Use of the manual tools greatly increases the amount of force applied and movement of the patient, especially in the case of a saw where the patient's head is likely to shake and move relative to the clamp and reference frame.

Tissue Loss

An unavoidable consequence of surgical intervention is the loss of healthy and pathological tissue. Since the overall goal of an image-guided procedure is to minimize trauma and loss of healthy tissue, the effects of tissue loss can have a serious effect on brain shift depending on the strategy used. Nabavi *et al.* (Nabavi et al. 2001) use intraoperative MRI over the course of an operation to show the effects of tissue loss and time on brain shift. Their study powerfully demonstrates how minimally invasive removal of tumour tissue can cause unsupported surrounding tissue to sag due to the forces of gravity. Furthermore, as the surgery progresses the surrounding tissue is affected by swelling, fluid loss and other surgical interactions.

Fluid Loss

When considering fluid loss and the relationship with brain shift there are mainly two fluids of concern: blood and CSF. The loss of blood is generally an insignificant factor since avoiding excessive bleeding is a major priority during surgery and strategies for preventing blood loss

throughout the procedure are in place. The more important fluid to consider is CSF. For many types of surgery, CSF is purposefully evacuated to allow for brain relaxation and less pressure or retraction. This is achieved within the skull or by using cranial or lumbar drains resulting in brain shift relative to the preoperative images. CSF loss can happen through many different avenues and affects the way brain tissue moves within the skull. Elias *et al.* (Elias, Fu, and Frysinger 2007) attempted to model subcortical shift as a function of CSF loss. They proposed a linear regression model based on measurement of patients undergoing DBS where CSF loss was the main contributor to shift. They showed that a loss of 20 cm^3 of CSF results in a shift of the anterior commissure by approximately 2 mm. They also report that the shift happened posteriorly (as measured on frontal cortex) and that volume of pneumocephalus was predictive of cortical and subcortical brain shift. The authors concluded that the volume of postoperative pneumocephalus approximates the volume of CSF lost during surgery and therefore can be used to estimate the shift associated with it. A primary reason that brain deformation is often in the direction of gravity with CSF loss is due to the loss of the homeostatic neutral buoyancy; with the reduction of buoyancy forces, the brain begins to deform under its own weight. The link between these two factors is an important tool when developing biomechanical, or predictive models of brain deformation

Mannitol

Often in neurosurgical interventions it is of interest to reduce intracranial pressure that has been amplified by tumour position, midline shift, or other trauma related to the surgery. The most common drug used for this is Mannitol. Lowering intracranial pressure is facilitated by hyperventilation that decreases the $PaCO_2$ and substantially decreases brain volume. Mannitol was first introduced in neurosurgery by Shenkin *et al.* in 1962 (Shenkin, Goluboff, and Haft 1962) because it is confined in the extracellular space, nontoxic, and is rapidly excreted by the kidneys. Since Mannitol does not cross the blood brain barrier, an elevated plasma osmolality due to an infusion of hypertonic mannitol is effective in removing fluid from the brain and can thus be also classified in creating brain shifts related to fluid loss. The use of Mannitol, however, inevitably changes the conformation of anatomy relative to the preoperative images being used for navigation that were acquired under different intracranial pressure. In situations where high levels of intracranial pressure or large amounts of edema are present Mannitol will be used regardless of the resulting 14euronavigation inaccuracies. However, during instances where it is not necessary it may be avoided to minimize brain shift (Benveniste and Germano 2005).

Tumour Type

Until recently, the primary cause of brain shift was believed to be gravity. As more sophisticated imaging, processing, and navigation techniques were developed and a drive for increasingly higher accuracy emerged, many other contributors were exposed. A surprising finding was that the type of tumour could affect the underlying shift. In many cases – as with any craniotomy – the brain will tend to herniate out of the defect to a degree dependent upon pathology thus creating complex and variable shifts. Dorward (Dorward et al. 1998) is one of the first and only studies that investigated brain shift based on tumour type. They observed unique patterns of shift between different tumour groups with a significantly greater shift at depth for meningiomas compared to gliomas and significantly less shift in skull base cases than other groups. Ohue (Ohue et al. 2010) reported on the overall difference in shifts between gliomas, meningiomas and other tumour groups, saying that gliomas tend to shift the most frequently and the most

unpredictably throughout surgeries, while meningiomas shift less compared to the two aforementioned groups. The reasons for these differences are not well understood and demonstrate the need for further validation before stronger generalizations can be made. Another important aspect when considering lesion type is the presence and type of edema, or perilesional edema. The presence of edema can have an important effect on the direction of shift and would be a meaningful parameter in the perspective of informing predictive modeling methods, taking into account the type of lesion and its associated edema. These results highlight the need for more studies investigating what specific factors cause such differences and if there are any surgical strategies that can be used to minimize the shift.

MEASUREMENT OF BRAIN SHIFT

As the use of 15euronavigation became more prevalent and widespread in neurosurgical interventions, the need for measuring the origins of inaccuracies caused by brain shift also became important. With the effects of brain shift making 15euronavigation systems unreliable for a large part of surgery, many investigators developed techniques to measure the subsequent shifts while attempting to attribute their cause. In order to assess the magnitude of brain shift there have been two main approaches; i) direct measurements performed in the physical space of the patient and ii) analysis of preoperative images with intra- or postoperative images combined with a registration procedure. In Table 2 we provide a summary of the different quantitative measurements of brain shift by different investigators in the literature that shows that there is no universal measurement technique or standard when quantifying the brain shift phenomenon and thus the degree of shifts varies largely between investigators. In the following subsections we describe the work and methods done in each of the studies in Table 2.

Table 2: Reported measurements of location and amount of brain shift

Reference	Method	Measurement Locations	Mean Brain Shift (mm)	Max Brain Shift (mm)
Kelly 1986 (Kelly et al. 1986)	Direct Measurement	cortex	"several mm"	
Nauta 1994 (Nauta 1994)	Direct Measurement	Tumour centre	"in the range of 5 mm"	
Hill 1998 (Hill et al. 1998)	Direct Measurement	dura	1.2	10
		cortex landmarks	5.6	
Roberts 1998 (Roberts et al. 1998)	Direct Measurement	global	10.9	24.6
Dorward 1998 (Dorward et al. 1998)	Direct Measurement	cortex (before resection)	4.6	12
		cortex (after resection)	6.7	
		tumour margin	5.1	16.5
Reinges 2004 (Reinges et al. 2004)	Direct Measurement	cortex (before resection)	6.1	14.3
		cortex (after resection)	6.6	15.2
Ganser 1997 (Ganser et al.	iMRI	cortex surface	20	22

1997)				
		lateral ventricles	5	7
Maurer 1998 (Maurer et al. 1998)	iMRI	ventricle volume	12%	40%
Nimsky 2000 (Nimsky et al. 2000)	iMRI	Cortex	8.4	23.8
		Deep Tumour	4.4	30.9
		Midline	0.1	5.9
		Ventricles	2.1	8.0
		tumour margin	4.4	30.9
Nabavi 2001 (Nabavi et al. 2001)	iMRI	cortex		50
Ferrant 2002 (Ferrant et al. 2002)	iMRI	cortex landmarks	4.5	8.4
Trantakis 2003 (Trantakis et al. 2003)	iMRI	tumour margin	19	25
Clatz 2005 (Clatz et al. 2003)	iMRI	tumour landmarks	3.8	13.2
Bucholz 1997 (Bucholz et al. 1997)	iUS	Various anatomical landmarks	5.0 (varies by structure)	12.6
Jodicke 1998 (Jodicke et al. 1998)	iUS	cortex landmarks	“several mm”	
Comeau 2000 (Comeau et al. 2000)	iUS	cortex landmarks	“brain sinking"	
Keles 2003 (Keles, Lamborn, and Berger 2003)	iUS	tumour margin (mannitol)	4.8	9
		tumour margin (no mannitol)	1.2	2.3
Letteboer 2005 (Letteboer et al. 2005)	iUS	cortex (∥ gravity, before dural removal)	3	9
		cortex (∥ gravity, after dural removal)	3.2	12.5
		cortex (⊥ gravity, before dural removal)	7.5	9
		cortex (⊥ gravity, after dural removal)	8.9	10.5
Reinertsen 2007 (Reinertsen, Lindseth, et al. 2007)	iUS - Doppler	Cerebral vessels	7.3	9.7
Ozawa 2009 (Ozawa et al. 2009)	iMRI - DTI	pyramidal tract	4.6	8.7
Ohue 2010 (Ohue et al. 2010)	iUS	Tumour margin (before dural removal)	3.4	10.8
		Tumour margin (during	8.5	19

		tumour removal)		
		Sulci (before dural removal)	3.9	9.1
		Sulci(during tumour removal)	9.1	19
		Third ventricle (before dural removal)	3	9.5
		Third ventricle (during tumour removal)	6.4	16.3
		Lateral ventricles (before dural removal)	3.3	6.6
		Lateral ventricles (during tumour removal)	8.2	19.3
		falx (before dural removal)	1.5	4
		falx (during tumour removal)	2.9	8.1
Ivan 2014 (Ivan et al. 2014)	iMRI	tumour centre	2	10.1
Mohammadi 2015 (Mohammadi et al. 2015)	iUS + Stereovision	Cortical surface	Not reported[3]	Not reported[3]
		Tumour (at depth)	Not reported[3]	Not reported[3]
Chen 2011 (Chen et al. 2011)	Laser Range Scanner	Homologous points on cortex	11.9	22.9
Simpson 2014 (Simpson et al. 2014)	Laser Range Scanner	Distance from tumor to resection cavity (points)	7.6	22.3
Miga 2015 (Miga et al. 2015)	Laser Range Scanner	Cortical surface points	10.1	21.3

Non-Image Based Measurements

Before intraoperative imaging was integrated into neuronavigation systems, investigators interested in measuring brain shift relied on rudimentary direct measurement techniques. As mentioned earlier, Kelly (Kelly et al. 1986) first measured brain shift as the *dislocation* of steel balls during volumetric stereotaxy. The most intuitive and common approach among direct measurements is to use a pointer device with the applied navigation system to measure the distance between certain structures in the physical and virtual spaces. The first report of brain shift in a conventional image-guided neurosurgical system was presented by Nauta (Nauta 1994) through direct measurement of the centre of a tumour using a ruler measuring shifts "in the range of 5 mm". Hill (Hill et al. 1998) measured brain surface motion twice during surgery by collecting a cloud of points, first after opening the dura but before resection by placing the probe on the dura, and then on the brain surface. They report the measurements being approximately an hour apart and they observed mean displacements of the dura and brain surface of 1.2 mm and 5.6 mm respectively with maximum displacements greater than 10 mm in a third of the patients. Roberts (Roberts et al. 1998) also directly measured shift by comparing the three-dimensional coordinates of cortical features, such as arterial or venous branch points, obtained with a neurosurgical microscope at different time points in surgery. Their results showed a mean displacement of 10 mm in the dominant directional component and therefore shift/displacement was attributed to gravity. They conclude that brain shift is gravity dominated and independent of

[3] The authors only provide the best registration error results for their measurement and fail to provide the magnitude of shifts corrected.

the size and orientation of cranial opening. Dorward (Dorward et al. 1998) used a different strategy in the evaluation of brain shift of different lesion types. They measured the offset between the centre of the planned craniotomy, the cortical surface at the centre of the dural opening and the deep tumour margin using a caliper tool. They reported a mean shift of 4.6 mm from the cortical surface before resection, 5.1 mm for the deep tumour margin and 6.7 mm for cortical shift after resection. They conclude that the shift is dependent on the presence of edema, lesion volume and lesion type with each type of lesion having unique patterns of shift. This secondary shift post-resection is very unpredictable and can be attributed to the brain tissue surrounding a glioma being edematous causing it to shift back towards the resection cavity. They also report that shift at depth is more severe in meningiomas than gliomas. Reinges (Reinges et al. 2004) measured the displacement of 2 – 3 superficial and subcortical landmarks using the tracked surgical pointer. They report a mean displacement of 6.1 mm across patients with a maximum of 14.3 mm after dural opening and mean of 6.6 mm with a maximum of 15.2 mm after resection. They reported that shifting of superficial landmarks exceeded subcortical structures and concluded that due to the heterogenous nature of lesions it is unlikely that preoperative prediction will ever be able to fully compensate for total intraoperative brain shift. Studies based on direct measurement of brain shift share a common characteristic, mainly that the resulting brain shift is reported as the localization error of a pointer or measuring tool. While efficient and useful, these methods are restricted to selective points and accessible structures in the operating field, are usually sparse in terms of the total number of quantifiable points, and are further limited by the precision of the navigation system.

Intraoperative Magnetic Resonance Imaging

Intraoperative MRI (iMRI) is one of the most widely used methods of intraoperative imaging for measuring brain shift and updating neuronavigation images and plans based on preoperative data. Brain shift in these types of studies are usually reported from analysis of the transformation determined from a registration procedure between preoperative and intraoperative images or as the movement of specific landmarks after a registration procedure. In this section we will describe studies focused on the measurement and characterization of brain shift using iMRI. The reader interested in the overall clinical impact of iMRI within functional navigation is directed to Kuhnt (Kuhnt, Bauer, and Nimsky 2012).

One of the earliest reports of using iMRI to quantify brain shifts came in Ganser (Ganser et al. 1997). In this study, a low field (0.2 T) iMRI was used to acquire intraoperative data and registered with preoperative navigation data using the chamfer matching technique (van Herk and Kooy 1994). The authors reported shifts of 20 mm at the surface of the cortex and 6 – 7 mm at the interhemispheric fissure and the lateral ventricles. This study, being one of the first of its kind, motivated the use of iMRI for brain shift measurement and compensation. Maurer (Maurer et al. 1998) reported on the volume change in ventricles of up to 40% using a 1.5 T iMRI scanner in a series of 6 patients using a rigid body transformation based on maximization of mutual information. Nimsky (Nimsky et al. 2000) provided one of the first large scale studies ($n = 64$) using iMRI to correct for brain shift using a 0.2 T open configuration MRI. Their corrections were based on using a rigid registration method and they reported shifts of up to 24 mm on the cortex and exceeding 30 mm for deep tumour margins. They also reported the significance of craniotomy size, resection volume, patient position, and tissue characteristics on brain shift on a patient-by-patient basis. Nabavi (Nabavi et al. 2001) conducted one of the most influential

studies using iMRI to examine the effects of brain shift on the accuracy of neuronavigation systems. In their study, serial 0.5 T iMRI images were taken to allow comprehensive sequential descriptions of the different direction and magnitudes of brain shift during a surgical procedure, demonstrating shifts up to 50 mm. This study not only highlighted the necessity for intraoperative updating of navigation images but also underscored the highly complex nature of brain deformations at different time points in surgery. Nimsky (Nimsky et al. 2001) reported on the importance of correction of brain shift with iMRI for complete resection in tumour surgeries. In 14 of the 16 cases investigated, brain shift measurement and correction led surgeons to continue tumour resections that had been deemed complete. This report is one of the earliest quantifications of how compensation of brain shift can lead to visualization of residual tumour and improved tumour resections and furthermore, how accurate up-to-date neuronavigation is essential. As further studies were published it became evident that more sophisticated techniques for measuring shifts accurately were needed. Ferrant (Ferrant et al. 2002) combined iMRI with deformable surface matching and a linear finite element elastic model to quantify shifts at different time points in surgery. They characterized brain shift after opening of the dura, at different stages of tumour resection and during brain swelling. Their reports, based on the movement of manually identified landmarks, found shifts of 0.6 – 8.4 mm, depending on the location and the time point of the measurement. The measurements were limited both by the resolution of the images as well as the localization error of the manually identified landmarks. Hartkens (Hartkens et al. 2003) provide an insightful analysis of brain shift using iMRI and nonrigid registration based on the ventricle volumetry. Prior to this study, gravity was thought to be the primary indicator of brain shift direction. Hartkens *et al.* however, used nonrigid deformation fields to show that the direction of brain shift is a result of the interplay between gravity, resection boundary conditions and fluid pressure; CSF loss and the direction of gravity alone are not adequate for accurate prediction. Trantakis (Trantakis et al. 2003) investigated the extent of brain shift over time and as a function of tumour removal. Using a 0.5 T iMRI combined with a nonlinear registration procedure based on matching segmented tumour volumes in images, they measured shifts of up to 25 mm. They described a similar effect with time as originally reported by Nabavi (Nabavi et al. 2001). An interesting finding is that brain shift due to tumour removal was generally maximal at the measurement when only 21% - 46% of the tumour had been removed and that subsequent shift after continuing resection did not contribute to the majority of the total shift. Clatz (Clatz et al. 2005) investigated the use of a complex nonlinear registration model in a retrospective study to update preoperative navigation images with iMRI. The main advantage of their approach is that it is completely automated in contrast to previous studies. They measured brain shifts of up to 14 mm based on the displacement between 54 landmarks around the segmented volume of the tumour being operated. In a different approach, Ozawa (Ozawa et al. 2009) attempted to estimate brain shift as the movement of the pyramidal tract using diffusion weighted imaging iMRI during resection of tumours. They measured shifts of 0.5 mm to 8.7 mm due to resection that were larger in the ipsilateral side of the tumour. In a more recent study, Ivan (Ivan et al. 2014) investigated the effect of burr hole techniques in neurosurgery in causing brain shift. Their measurements were based on the movement of certain regions of interest from the magnetic isocentre using iMRI. They report shifts averaging 1.4 mm (and up to 10.1) mm among a wide distribution of structures in the brain. They conclude that with even small burr hole procedures, brain shift is a strong influencing factor and highly unpredictable. A major drawback of iMRI methods stems from the cost and time it adds to a specific procedure, however, an additional concern stems from the fact

that confusing contrast can be introduced from surgery (Knauth et. Al 1999). This may lead to a difficulty in intraoperative diagnosis that could inflate navigation error and must be carefully evaluated when used.

Intraoperative Ultrasound

An alternative to iMRI is the use of intraoperative ultrasound (iUS). Unlike iMRI, ultrasound is easy to use, is low-cost and widely available. Bucholz (Bucholz et al. 1997) provide the first documented quantitative measurement of brain shift using an iUS probe. They investigated the use of iUS during hematoma and tumour neurosurgery measuring shifts at different anatomical structures following a registration procedure. They measured shifts of up to 12.6 mm among a various range of shifts for different structures. Jödicke (Jodicke et al. 1998) also provide one of the earliest accounts of iUS coupled with a registration procedure for measuring brain shift. While they reported no quantitative measurements they described the shift between contoured landmarks in MRI and iUS images. Comeau (Comeau et al. 2000) described the use of a iUS and neuronavigation system and its applicability for measuring and correcting for brain shift intraoperatively. Although no quantitative measurements were provided, the authors qualitatively described the sinking of the cortical surface, contraction of the ventricular system and shift of the tumour in the reported cases. The authors commented on the limitations of their system related to accuracy of the ultrasound calibration (1 – 2 mm) and the poor quality of the iUS images in regards to the ability to accurately determine anatomical features between the iUS and preoperative MRI. Keles (Keles, Lamborn, and Berger 2003) used iUS to measure brain shift throughout tumour resection procedures. Measurements were based on the location of the tumour relative to the cortical surface as well as the location of the cortical surface relative to its original position. Patient-to-image registration was only performed once in this study and the accuracy of the registration was assessed at different times during surgery by looking at the deviation of certain structures that the authors deemed stable and not affected by shift. The authors reported shifts of up to 9.0 mm for patients who received Mannitol and only up to 2.3 mm for those who did not. Contrary to other published findings they found that tumour volume did not have an effect on the amount of brain shift. Furthermore, they reported that age was a factor in determining the extent of brain shift. Letteboer (Letteboer et al. 2005) used 3-D ultrasound to measure rigid brain shifts prior to removal of the dura and after opening the dura. They measured mean shifts of 3.0 mm and 7.5 mm in the directions parallel and perpendicular to gravity before dural opening and an addition shift of 0.2 mm parallel to gravity and 1.4 mm perpendicular to gravity after dural opening. This study shows the compounding effects of brain shift before the surgical intervention has even taken place. Rasmussen (Rasmussen et al. 2007) used intraoperative ultrasound to map shifts of DTI MRI image sets. They report that the shifts were in different directions for each patient investigated and were difficult to predict. Reinertsen (Reinertsen, Descoteaux, et al. 2007; Reinertsen, Lindseth, et al. 2007; Reinertsen et al. 2014) investigated the use of intraoperative Doppler ultrasound to measure brain-shift. After a Doppler acquisition, the visible vessels were segmented and then registered with segmented vessels from a MR angiography (MRA) image. The authors reported shifts of up to 9.7 mm. More recently, Mohammadi (Mohammadi et al. 2015) used Doppler ultrasound in combination with stereovision to estimate brain shift. The stereovision was used to estimate displacement of the cortical surface and the ultrasound was used to measure the deformation of internal vessels using a newly developed registration method described as finite element drift. The authors only present the best registration error results of their animal experiments and thus make it difficult to

objectively evaluate the usefulness of their proposed method since the degree of shift corrected is not reported. Ohue (Ohue et al. 2010) evaluated the effect of brain shift using iUS at different time points during surgery as well as at a variety of locations. The iUS images were overlaid on the preoperative images and the maximum distance between structures of interest was reported. Before dural incision they measured shifts of up to 10.8 mm, 9.1 mm, 9.5 mm, 6.6 mm and 4.0 mm for the tumour margin, sulci, third ventricle, lateral ventricles, falx and tentorium respectively. They also reported that shift increased up to 19.3 mm both during and after tumour removal. This study is one of the few to correlate shift of tumour margins with different types of tumour. They found that gliomas have the largest total shift (up to 19 mm) and initial shift before dural incision (up to 11 mm) while meningiomas experience less total shift and other tumours experience even less shift before dural incision. Intraoperative US imaging has proven to be a valuable alternative to iMRI and as outlined here has been successful in characterizing brain shift.

Other Image Based Methods

While iMRI and iUS make up the majority of image-based techniques for measuring brain shift, several groups have quantified the effects of brain shift using laser range scanners (Sinha et al. 2005; Sinha et al. 2006; Ding et al. 2007; Chen et al. 2011; Simpson et al. 2014; Miga et al. 2015), and stereo cameras (Faria et al. 2014; Sun, Lunn, et al. 2005; Sun, Roberts, et al. 2005). A primary use of laser range scanners is to collect sparse intraoperative data to assist model-based compensation methods. There are, however, recent studies that perform physical measurements using laser range scanner vessel tracking (Chen et al. 2011; Simpson et al. 2014; Miga et al. 2015). The output data are textured point clouds within the field of view that can give a 3D measurement with known correspondence. Results for stereo cameras are also generally presented as point clouds or approximate surface data that are compared to the last prior measurement to help a model predict further shifts or compensate for the underlying shifts. Many of the results for this type of work are combined with results of modeling methods discussed in the next section. Finally, while not used to measure or compensate for brain shift, some authors have tried to circumvent the brain shift issue through the use of fluorescence imaging. This technology has been recently reviewed by Pogue (Pogue et al 2010) and this kind of imaging allows for intraoperative tumour delineation by having an active marker visually present to guide resection in the presence of uncorrected brain shifts within the neuronavigation system. This technology represents a different avenue for dealing with brain shift when accurate navigation cannot be relied upon.

COMPENSATION OF BRAIN SHIFT

When discussing methods for compensating for the effects of brain shift in neuronavigation we find two main streams in the literature; methods that focus on the registration of intraoperative images and methods where intraoperative information is sparse or absent and thus the focus on modeling the shift through biomcechanial or predictive models. In many of the different methods a combination of approaches are used and each has different benefits and drawbacks. Registration methods obviously require the use of intraoperative imaging that can add to operation time and to the complexity of a surgery. However, to date they are currently the most accurate way to compensate for brain shift. Modeling methods based on physics priors usually take a registration strategy in order to analyze deformations that may be imposed on preoperative images. These are generally rather time consuming strategies that can often result in high

computational costs but can also be highly accurate. Methods based on predictive modeling have the advantage of needing very little or no intraoperative information but a main drawback of these methods is that changes and effects caused by surgery are not taken into account. These methods are detailed below.

Registration

Registration creates a mapping between brain shift invalidated preoperative images and brain shift corrected intraoperative images. There are many different approaches to the registration of medical images that aim to exploit either the differences or similarities of the images being aligned. Medical image registration is a very large field of research and there has been a lot of work done in the context of brain imaging in general as well as for brain shift compensation in particular. As the details of registration methods are not intended to be the focus of this review interested readers are directed to Hill (Hill et al. 2001), Maintz (Maintz and Viergever 1998), and Oliveira (Oliveira and Tavares 2014) for a general overview and perspective of medical image registration, to Sotiras (Sotiras, Davatzikos, and Paragios 2013) for a review of deformable registration methods, and finally, to Crum (Crum et al. 2003) for notions related to the quality of non-linear fits in medical image registration. The following section addresses specific articles focused on biomechanical models used in registration for the correction of brain shift and encompasses registration details that are more relevant to this review.

Biomechanical Modeling

Development of accurate biomechanical models is important to compensate for brain displacement and is an ongoing focus of a large portion of the research community. More accurate and more robust biomechanical models in conjunction with complex registration methods will allow for faster and more accurate modeling and correction of brain displacement. Most of the research works that have been done in biomechanical modeling of the brain tissue for this purpose are not completely independent of the registration methods. The works that were reviewed in this section, however, relate to articles that focus on the biomechanical modeling aspect of the brain rather than registration.

The applied methods in most of these works were based on linear elastic (considering small tissue deformation) or hyperelastic (considering large tissue deformation) model of the brain tissue (Miga et al. 2001; D'Agostino et al. 2003; Wollny and Kruggel 2002; Soza et al. 2003; Winkler et al. 2005). DeLorenzo (DeLorenzo et al. 2012) developed a linear elastic model of the brain based on the known material properties of the brain tissue to infer its volumetric deformations. Their method does not require any knowledge about the intra-operative conditions and was based solely on pre-operative conditions. Karami (Karami et al. 2009) developed a micromechanical hyperelastic model of the brain white matter under large deformations. Miga (Miga et al. 1999) and Paulsen's (Paulsen et al. 1999) simulations for obtaining the brain displacements were based on a 3D finite element model. The brain tissue biomechanical properties required for this finite element model were obtained ex-vivo using animal brain tissue that mimics human brain tissue. Hamidian (Hamidian et al. 2010) used information derived from sparse low-resolution images and considered both linear and nonlinear biomechanical models for finite element analysis to determine model parameters for compensating for brain displacements. In an attempt to have a more accurate finite element analysis, Lunn (Lunn et al. 2005) introduced the adjoint equation method that describes a technique for estimating the unknown boundary

conditions and internal forces that are necessary to combine the model information with the preoperative and intra-operative data. They have improved their initial work by developing guidelines which indicate the optimal strategy for selecting model parameters (Lunn et al. 2006).

Since the brain tissue was considered to be pure elastic in these models, the viscosity behavior of the brain tissue was not taken into account in these works. More complex approaches are based on viscoelastic models of the brain tissue that simulate rigid, elastic, and fluid regions independently as in Hagemann (Hagemann et al. 1999; Hagemann, Rohr, and Stiehl 2002). In addition to the viscosity properties, a more complete biomechanical model of the brain requires information about brain tumours. Tumours with different biomechanical properties than normal brain tissue add some complexities to the brain biomechanical modeling. Becker (Becker et al. 2010) presented a biomechanical model that takes into account the mass effect of tumour expansion in brain displacement. Mang (Mang et al. 2012) presented a framework for modeling the tumour-induced brain deformations a *a priori* knowledge for non-rigid image registration. The model is based on an initial boundary value problem that defines the progression of primary brain tumours governed by proliferation of cancerous cells into the surrounding healthy cells.

Predictive Modeling

While compensating for brain shift with intraoperative image registration has seen its share of success, a different avenue based on mathematical modeling has also been used in the field. An important prerequisite of this strategy is having data containing general information about the characteristics of the brain shift (Hastreiter et al. 2004). These methods focus mainly on preoperative images due to either absent or sparse intraoperative data. One type of modeling strategy is focused on *predicting* the deformation to correct preoperative images (Skrinjar, Nabavi, and Duncan 2002; Dumpuri et al. 2007; Dumpuri et al. 2010; Chen et al. 2013; Hu et al. 2007; Zhuang et al. 2011; Joldes et al. 2009; Joldes, Wittek, and Miller 2009). Skrinjar (Skrinjar, Nabavi, and Duncan 2002) developed a biomechanical model-based approach that predicts brain shift by comparing a damped spring-mass model and a model based on continuum mechanics that is partially driven by information from the exposed brain surface. Dumpuri (Dumpuri et al. 2007) introduced an atlas-based method to predict brain shift. The forward-run model solutions were constructed with a variety of different driving conditions based on surgical conditions such as head orientation and fluid loss. In Dumpuri (Dumpuri et al. 2010), the authors validated their proposed strategy showing the ability to recapture 85% of the mean subsurface shifts as measured by postoperative imaging. Chen (Chen et al. 2013) extended the work on atlas-based brain shift prediction by modeling tissue retraction within the brain shift compensation framework. Their work, which built on previous modeling of tissue retraction (Miga et al. 2001; Platenik et al. 2002), considered retraction as an active component of deformation. However, they did not precompute the potential deformation caused by retractors but rather computed the deformation based on the tracked location of a retractor intraoperatively. Hu (Hu et al. 2007) developed a 3D patient-specific finite element brain model based on a 50^{th} percentile male template with detailed anatomical structures. Finite element models were used to predict gravity induced brain shift based on different orientations of the patient's head. Zhuang (Zhuang et al. 2011) also used a finite element linear elastic model that used sparse intraoperative data from cortical surface tracking by a 3D laser range scanner to predict global brain shift. Joldes (Joldes et al. 2009; Joldes, Wittek, and Miller 2009) used patient-specific biomechanical models implemented using specialized nonlinear finite element FE techniques that took into account

material and geometric nonlinearities in order to predict brain shift. To date, the work done on predictive modeling for the compensation of brain shift is still relatively sparse. However, it is a fast growing field and can be especially useful as a complimentary tool with medical imaging processing techniques (Bucki, Lobos, and Payan 2007) when conducting non-rigid registration within the real time constraints of neurosurgery.

DISCUSSION

It is evident from the work described above that brain shift is a very complex problem that has widespread causes ranging from the limitations of the technical components of the neuronavigation hardware, surgical causes from equipment resection of tissue and loss of fluid, as well as biological effects related to drug administration and the type of brain tumour present. The work done to describe the contributions from these different factors has led to numerous strategies to quantify the contribution of each of the factors to inaccuracies in neuronavigation. Strategies for measuring shift have ranged from direct measurement to complex intraoperative imaging and registration techniques that can provide up-to-date images for navigation. Some of the most exciting work in the field, which has seen growing success over its short lifetime, is the new strategies that simulate brain shift using mathematical models.

As the field of image guided surgery grows and expands to many applications beyond neurosurgery, it is important to keep a cautionary perspective on the assumptions that 'state-of-the-art' image guided neurosurgery techniques relies on; specifically, a rigid reference system. The majority of human anatomy is not encased in a rigid container like the brain and skull and thus many IGNS practices may translate poorly to other major organ environments. For image guidance in other soft tissues, the idea of rigid 'reference-to-patient' has moved towards real-time organ-to-organ registrations and real-time ultrasound and microscope tracking that build a frame of reference as they go. As the techniques for image guided neurosurgery move forward, the concept of patient tracking and patient-to-image registration could evolve into something incredibly different than that described here. These differences will also shape the way we investigate, measure, and compensate for brain shift, and what we learn from this will need to be put into perspective when trying to expand techniques and measurements to other fields of soft-tissue guidance. Thus, the proposed taxonomy relating to registration and tracking should not be considered so rigid as to limit creativity when investigating brain shift, but as a historical categorization of what is currently the best available for reference in the field of neurosurgery and not necessarily for all fields of image guidance.

There are still many challenges to overcome to complete understanding of brain shift so that accurate predictions and correction of the phenomenon is facilitated. While it is widely accepted that one of the biggest uncontrollable causes of brain shift is gravity, there are many additional factors that until recently have been overlooked. As the strategies for compensation become more complex and effective, the contributions of the smaller effects will need to be better understood. There is a lack of studies focused on isolating the way in which single factors contribute to brain shift and this has led to results being reported in a non-systematic way with different authors attributing different effects to different features of the patient and environment. This leads to highly variable results that make reporting on brain shift difficult, resulting in difficulties in understanding that have led to limited generalization for strategies that model the phenomenon. There have only been a handful of reports correlating brain shift effects with

previously overlooked features such as tumour type (Dorward et al. 1998; Ohue et al. 2010) and patient position (Schnaudigel et al. 2010), as well as studies trying to model certain effects such as the loss of CSF (Elias, Fu, and Frysinger 2007). More often than not, the number of patients reported in these types of studies is relatively low for statistical modeling ($n < 50$). This means that it will be important that more studies are conducted in the future to confirm the reported factors and to precisely characterize their contributions. The need for characterization will be extremely important for predictive brain shift compensation strategies. The more information that is known about the underlying mechanisms of brain shift, the more likely these strategies will be to succeed in the future. Isolating independent factors is an extremely challenging problem especially when all studies focused on brain shift typically deal with a major pathology. While our recommendations here suggest looking beyond gravity, it is important to note that in even the most complicated predictive compensation methods (Dumpuri et al. 2010; Chen et al. 2013) the brain shift corrections imply equal parts gravity and mannitol in many cases as the primary match for brain shift. Therefore, understanding these more subtle contributions to the shifting phenomenon will allow us to capture closer to 100% of the total shift and is not intended to suggest that gravity is not responsible for a major component of the shift. An investigation of brain shift with healthy subjects could provide insight as to the influence of simple factors such as physical factors, patient position, gravity without tissue loss, and drug interaction, however, this is unfeasible on humans for ethical reasons but could be performed on animal models to help with the understanding of these phenomena. The study of DBS (Pallavaram et al. 2009; Petersen et al. 2010; Derrey et al. 2011; Takumi et al. 2013), may provide such insight as brain shift is prevalent but where its magnitude is much smaller

Many investigators have attempted to quantify brain shift through a variety of methods. The results reported are highly variable and susceptible to many different types of measurement errors. Quantifying brain shift is extremely difficult and there is a lack of consistent methods to report measurements. Many early techniques relied on direct measurement of shifts (Kelly et al. 1986; Dorward et al. 1998; Hill et al. 1998; Roberts et al. 1998; Reinges et al. 2004). This was done either through the reported location of the tracked surgical pointer or by the distance between landmarks on images. While these methods were important during the initial investigation of brain shift, they suffer from many localization errors that are difficult to quantify. For example, a tracked surgical pointer needs to be calibrated in order to determine the relationship between the tracking device and the tip of the pointer. This calibration is imperfect and may lead to errors of up to 0.6 mm (Gerard and Collins 2015) depending on the distance of the pointer from the reference frame and the tracking device. Localization error associated with manually identifying a landmark also plays a large role when considering direct measurement since it is unlikely that the desired location for measurement aligns perfectly with the chosen place for measurement (Fitzpatrick, West, and Maurer 1998).

Intraoperative imaging has seen a wide range of use in the last two decades with the primary focus being placed on iMRI and iUS. The benefit of intraoperative imaging is that it allows up-to-date visualization of patient anatomy. This is extremely important when investigating brain shift as it allows for both qualitative and quantitative investigation. As shown in the literature, iMRI is a very useful tool for intraoperative imaging (Kuhnt, Bauer, and Nimsky 2012). It offers high tissue contrast, is the same modality as most preoperative images facilitating comparison and has the ability to visualize tissue in many different ways due to the wide variety of imaging

sequences available. However, there are many factors that make this technology unavailable to most centres worldwide. The iMRI device is extremely expensive and requires a dedicated OR theatre, specialized tools that are non-magnetic and also specially trained staff for daily use (Kuhnt, Bauer, and Nimsky 2012). Another important factor is related to the amount of time that iMRI adds to a procedure, which is on the order of an hour or more per scan/use. The burdens associated with these requirements make it difficult for iMRI to become routine except in the largest leading academic centres. On the other hand, iUS has also been investigated for brain shift. Intraoperative US is relatively inexpensive and non-invasive and also does not require many changes to the operating room or surgical procedures (Unsgaard et al. 2002). The main challenge associated with iUS is relating the information to the preoperative imaging such as MRI. The alignment of iUS to MR images is a challenging task due to the widely different nature and quality of the two modalities. While voxel intensity of both modalities is directly dependent on the tissues imaged, US has an additional dependence on probe orientation and depth that can lead to intensity non-uniformity due to the presence of acoustic impedance transitions. Preoperative MR images allow for accurate and precise identification of tissue types, anatomical structures and a variety of pathologies such as cancers. Intraoperative US images are generally lower quality but have the ability to show different tissues, borders between tissues as well as the borders between lesions and healthy tissue. Many groups have worked on methods for incorporating iUS into image guidance (Smith, Frank, and Bucholz 1994; Lindseth et al. 2002; Unsgaard et al. 2002; Tuominen et al. 2003; Schlaier et al. 2004; Reinertsen and Collins 2006; Rasmussen et al. 2007; Mathiesen et al. 2007; White et al. 2009; Farnia et al. 2011; Mercier et al. 2011; Mercier et al. 2013; Farnia et al. 2014; Walkden et al. 2015). Since the focus of these studies was not on measuring brain shift, they are not reviewed in this paper. However, the interested reader is directed to these studies for a more comprehensive understanding of the use of iUS in IGNS. This review is intended to give a comprehensive overview of the scope of work done in regards to brain shift. There are several other works by authors exploring certain areas of some of the work presented here. The interested reader is directed to Miga 2016 (Miga 2016) for a thorough review of computational modeling for enhancing soft tissue image guided neurosurgery, and to Schulz 2012 (Schulz et al. 2012) for a broader scope of intraoperative image guidance in neurosurgery and its future direction.

Reports of measuring brain shift using intraoperative imaging have become the standard in much of the modern literature (Reinertsen et al. 2014; Clatz et al. 2005). Both iMRI and iUS suffer from different challenges when trying to quantify brain shifts. The link between intraoperative imaging and brain shift measurement is a registration procedure that relates intraoperative and preoperative images to one another. Many of the reported shifts are calculated from the transformations that map between two images at a specific location or at manually chosen landmarks on the images. Caution must be taken when using these methods to quantify brain shift since they are generally reported with some form of inaccuracy associated with the registration procedure as well as the model used to drive the registration procedure. Some authors take a simple approach using a rigid or linear transformation to match the images (Maurer et al. 1998; Nimsky et al. 2000). While a rigid transformation is satisfactory for quantifying certain factors of brain shift there are other factors that involve more complex movements that need nonlinear deformations to be correctly quantified. It is still unclear when and where linear vs. nonlinear deformation is necessary and this will be an important challenge that should be addressed in future studies. In addition to these technical challenges with

intraoperative imaging, iMRI and iUS can be bounded to a lower limit of accuracy based on the resolution of the acquired images which is generally on the order of 0.5 – 1.0 mm, however sub-voxel localization is possible in some situations. MRI can also suffer from many different geometric distortions (Caramanos et al. 2010) that create imperfect anatomical representation. Intraoperative US also suffers from several different sources of errors. Since an iUS probe is being tracked, the technical errors similar to those described for a tracked surgical pointer are also present (Comeau et al. 2000). In addition, an iUS probe must be calibrated for different depths and speed of sound in different material. While the problem of US calibration has been widely investigated, calibration errors on the order of 1.0 – 2.0 mm are commonly reported which increases the lower bound of error in the alignment of images (Mercier et al. 2005).

With some of the outlined drawbacks of many intraoperative quantification methods, a new field based on predictive modeling has become increasingly popular. There is a major limitation for studies reporting on brain shift measurement based on postoperative imaging data as seen in many authors employing predictive modeling strategies. Generally postoperative imaging is done within 48 hours of surgical intervention and several factors may lead to misrepresentation of brain shift from its true intraoperative nature, most importantly that resection cavities can decrease by up to 50% from the post-op MRI to the next day MRI. For many of these cases the head orientation from the OR and during acquisition of postoperative imaging will cause an additional or a different shift of tissue not consistent with what would be measured intraoperatively. Furthermore, the viscoelastic nature of the brain and the regeneration of CSF within the brain are factors that would contribute towards recovery of some of the intraoperative brain shift giving an inaccurate measurement of the observed shifts. While these studies are important for proof of concept of a forward planning and predictive computational models, the results should be interpreted with caution until intraoperative validation studies have been performed. As with other techniques that quantify shift, for this fast growing method to continue seeing success, improved characterization of individual factors contributing to brain shift will be essential.

CONCLUSION

We presented a review of the research evaluating the causes, measurements and correction methods of brain shift in neuronavigation with a newly proposed taxonomy for classifying the different types of studies. With the increasingly ubiquitous use of neuronavigation systems in neurosurgical interventions, the need for highly accurate information has become of utmost importance. Brain shift is a well-documented phenomenon and one of the largest contributors to inaccurate neuronavigation. While some factors are avoidable, many others can be minimized and caution should be taken throughout procedures using neuronavigation in order to maximize accuracy. Techniques based on intraoperative imaging have highlighted some of the general sources of these shifts but have also exposed limitations in regards to best attainable accuracy. Predictive modeling, which in its short life span has already seen some success, suffers from high computational costs as well as the need for a variety of specific model parameters that are currently unavailable, limiting its upside. Due to the highly dynamic nature of brain shift throughout a surgical intervention the current methods for compensation only provide a small portion of the true underlying effect. Because of this, there is a strong need for more imaging studies attempting to quantify individual factors on the behavior of brain shift so that the

phenomenon can be more completely modeled and predicted. Furthermore, if predictive brain shift models are to be more successful and relied upon, concurrent studies with intraoperative imaging must be performed for more complete and extensive validation of these methods. With the proposed taxonomy, future studies of brain shift can be more elegantly classified in regards to what features of the phenomenon they are investigating and will be able to address areas that are currently poorly understood in order to solve the problem more completely.

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