

Diffusion tensor MRI of chemotherapy-induced cognitive impairment in non-CNS cancer patients: a review

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Abstract Patients with non-central nervous system cancers often experience subtle cognitive deficits after treatment with cytotoxic agents. Therapy-induced structural changes to the brain could be one of the possible causes underlying these reported cognitive deficits. In this review, we evaluate the use of diffusion tensor imaging (DTI) for assessing possible therapy-induced changes in the microstructure of the cerebral white matter (WM) and provide a critical overview of the published DTI research on therapy-induced cognitive impairment. Both cross-sectional and longitudinal DTI studies have demonstrated abnormal microstructural properties in WM regions involved in cognition. These findings correlated with cognitive performance, suggesting that there is a link between reduced “WM integrity” and chemotherapy-induced impaired cognition. In this paper, we will also introduce the basics of diffusion tensor imaging and how it can be applied to evaluate effects of therapy on structural changes in cerebral WM. The review concludes with considerations and discussion regarding DTI data interpretation and possible future directions for investigating therapy-induced WM changes in cancer patients. This review article is part of a Special Issue entitled: *Neuroimaging Studies of Cancer and Cancer Treatment*.

Keywords Diffusion tensor imaging · DTI · Chemotherapy · Cancer · Cognition

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Introduction

Due to earlier diagnosis and improved cancer treatments, the survival rate of cancer patients has increased significantly in recent years and the quality of life after treatment has now become an important area of research. It is well known that patients that have been treated with cytotoxic agents for non-central nervous system (CNS) cancers regularly report cognitive problems (Schagen and Vardy 2007; Ahles et al. 2010; Wefel and Schagen 2012; Jim et al. 2012). They typically experience subtle cognitive changes covering domains mainly involving memory, attention, processing speed, and executive functioning. These effects remain significant after controlling for related factors such as anxiety, fatigue, mood, and IQ (Wefel et al. 2010).

Despite the partial protection of the brain by the blood-brain barrier, chemotherapy could impair cognitive functioning through direct or indirect neurotoxicity, potentially damaging brain parenchyma and altering, for example, the white matter (WM) microstructural tissue properties. How particular chemotherapeutic agents can cross the blood-brain barrier remains a matter of debate. There is evidence, however, that a frequently used chemotherapeutic agent, 5-fluorouracil (5-FU), crosses the blood-brain barrier simply by means of diffusion (Bourke et al. 1973; Kerr et al. 1984). Nevertheless, the pathophysiology of this impaired cognitive functioning is still unclear and more research is needed to answer the question whether therapy-induced structural changes to the brain could underlay cognitive deficits in cancer survivors.

WM consists of bundles of tightly wrapped axons, surrounded by myelin sheaths, that connect different brain regions. The successful execution of complex cognitive tasks depends on the coordinated activity in distributed brain networks and the integrity of brain WM pathways to transfer the necessary information (neural signals) in a timely way (Engel et al. 2001). Damage to the WM pathways decreases the

efficiency of communication among neural systems, impairing cognitive processes. In this context, animal studies have reported damage to myelinated WM tracts of the central nervous system after systemic treatment with chemotherapeutic agents like 5-FU and methotrexate (Dietrich et al. 2006; Han et al. 2008; Seigers et al. 2009).

In contrast to the accumulating body of neuropsychological literature, imaging studies that relate cognition to brain structure in chemotherapy patients are scarce. The use of advanced MRI techniques combined with detailed cognitive assessment can offer new insights into the neural substrate of therapy-induced cognitive complaints in cancer survivors. Diffusion tensor MRI (DTI), in particular, is a good candidate technique to study potential chemotherapy-induced changes in WM in vivo as it can provide a non-invasive assessment of WM organization. DTI parameters are known to be sensitive to subtle changes in the microstructure of WM fiber tracts and have been linked with normal cognitive functioning in healthy subjects (Turken et al. 2008; Sasson et al. 2010) and impaired cognitive functioning in diseased subjects (Cho et al. 2008; Parente et al. 2008; Sage et al. 2009; Metzler-Baddeley et al. 2012a). Various studies also linked age-related cognitive impairment with DTI based measures (Grieve et al. 2007; Barrick et al. 2010; Charlton et al. 2010). As such, DTI is a promising technique to assess whether possible therapy-induced WM changes could explain the cognitive complaints in women after cancer treatment.

In this paper, we first review the basic concepts of DTI and how it can be applied to evaluate effects of therapy on structural changes in cerebral WM. In addition, we give an overview of previous studies that have used DTI to investigate impaired cognitive functioning in patients with non-

CNS cancer. Finally, we present several critical notes regarding data interpretation and provide guidelines and possible future directions for investigating therapy-induced WM changes in cancer patients.

Basic concepts of diffusion tensor imaging (DTI)

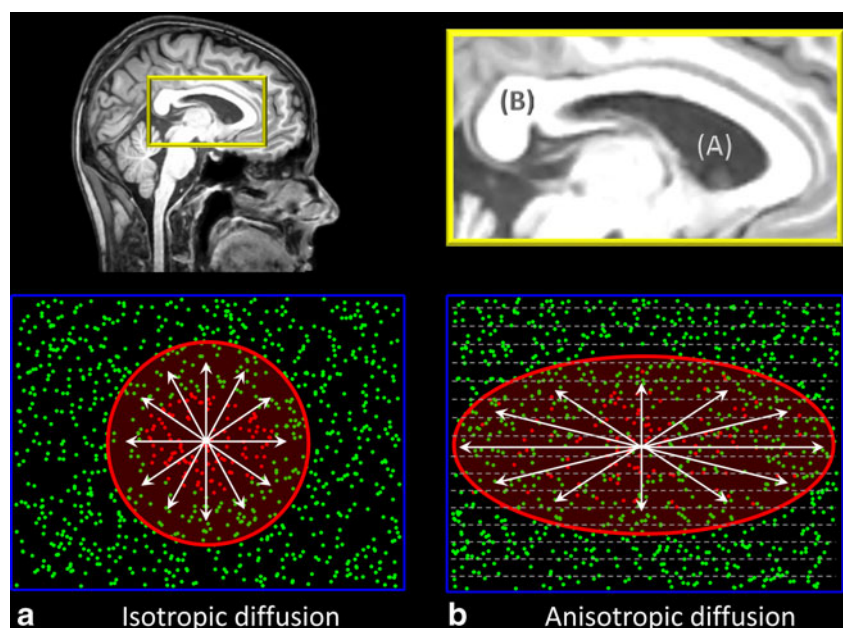
The diffusion principle

Diffusion is a phenomenon in which particles, driven by thermal energy, move from one place to another in an erratic random way. If these particles (e.g., water molecules) spread out with the same amount in all directions, such as, for instance, in cerebrospinal fluid (CSF), the diffusion is called “isotropic”. By contrast, diffusion is said to be “anisotropic” if there is a dominant orientation along which the particles prefer to move. In WM fiber bundles, for instance, diffusion is likely to be anisotropic as water molecules are less hindered by obstacles, such as axon walls and myelin sheaths surrounding the axons, along the fiber trajectory than perpendicular to it (Fig. 1).

Diffusion-weighted (DW) MRI

In diffusion weighted magnetic resonance imaging (DW-MRI) (Le Bihan et al. 1986) a “diffusion” gradient is applied that makes the MR signal sensitive to displacement of molecules in the direction of that gradient. If this gradient is oriented along the WM fiber pathway, the diffusion will be large, causing a high signal loss, whereas if oriented across the pathway, there will hardly be any signal attenuation as the diffusion will be small. Consequently, for WM

Fig. 1 Schematic representation of particles moving **a** “isotropically”, i.e., with an equal amount in each orientation (such as in cerebrospinal fluid regions); and **b** “anisotropically”, i.e., more pronounced along the left-right than the up-down orientation due to barriers as represented by the *dashed lines* (such as axonal membranes in, for instance, the corpus callosum)



fiber pathways the image contrast will depend on the orientation of the diffusion gradient that is used (i.e., anisotropy) (Moseley et al. 1990). For CSF regions, on the other hand, the image contrast will be the same irrespective of the diffusion gradient orientation.

The DW-MR signal reflects the relative degree by which molecules are hindered from diffusing along the orientation of the applied gradient. More specifically, a high intensity in a DW-MR image reflects a small amount of diffusion and vice versa. The apparent diffusion coefficient (ADC) quantifies the magnitude of diffusion that occurred along a particular diffusion gradient orientation and is derived from the DW-MR image and a reference image (i.e., the non-DW-MR image, also known as the “ $b=0$ ” image, in which no diffusion weighting has taken place). Figure 2 shows examples of (non-)DW-MR and ADC image maps.

From DW-MRI to DTI

Despite its ability to visualize the actual diffusion contrast, DW-MRI is not capable of quantifying diffusion anisotropy in an unambiguous way given the fact that the image contrast depends on the relative orientation between the tissue-of-interest and the applied diffusion gradient orientation. A major breakthrough in the field addressing this problem was presented by Basser et al., who introduced the diffusion “tensor” model (Basser et al. 1994)—hence the name diffusion tensor imaging (DTI). From this Gaussian model, DTI “microstructural biomarkers” can be derived that are invariant to the actual configuration of the applied diffusion gradients (discussed in the next section).

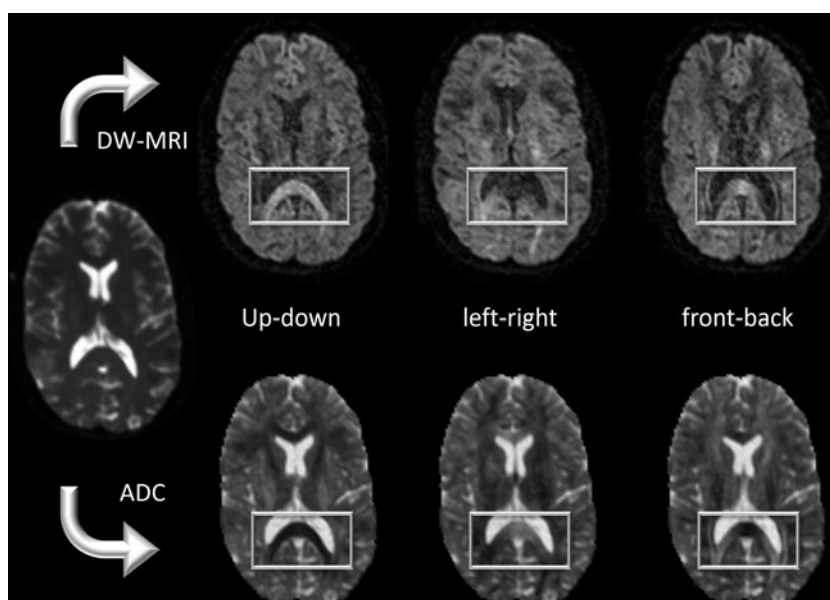
The only requirement imposed with DTI is that at least 6 DW-MR images (in addition to the “ $b=0$ ” image) need to be

acquired along non-collinear diffusion gradient orientations. In practice, however, more directions (~20 to 60) are typically used to increase the reliability of the diffusion tensor estimation (Jones & Basser 2004; Jones 2010b). From this diffusion tensor, which is basically a symmetric 3 by 3 matrix, eigenvalues and eigenvectors can be calculated which, in turn, can be interpreted geometrically as an ellipsoid (see Fig. 3). More specifically, the eigenvalues represent the magnitudes of the diffusion along the orientations of the associated eigenvectors, i.e. the principal axes of the ellipsoid.

DTI based measures

From the diffusion tensor, various scalar measures can be computed. The most common measures that have been used in clinical applications are derived from the eigenvalues and include mean diffusivity (MD), fractional anisotropy (FA), radial (also known as perpendicular or transverse) diffusivity (RD), and axial (also referred to as parallel or longitudinal) diffusivity (AD). Whereas MD, defined as the average eigenvalue (or the trace of the diffusion tensor divided by three), reflects the overall diffusion magnitude, RD and AD represent the average diffusion in the plane perpendicular to the first eigenvector (i.e., the average of the two smallest eigenvalues) and the amount of diffusion along the orientation of the first eigenvector (i.e., the largest eigenvalue), respectively (Basser 1995). The FA is defined as the ratio of standard deviation and root mean square of the eigenvalues and has a value range between zero (isotropic diffusion) and one (reflecting diffusion along a single axis). For example, the FA in the CSF, where the amount of diffusion will be the same in all directions, will be close to zero, whereas

Fig. 2 An example of an axial non-diffusion-weighted (DW) MR image (*left*), three DW-MR images (*top*), and their corresponding apparent diffusion coefficient (ADC) maps (*bottom*); each image is min-max scaled for optimal visualization clarity. Notice the difference in contrast in the white matter regions (“diffusion anisotropy”), such as the splenium of the corpus callosum (highlighted by the *white rectangles*). By contrast, cerebrospinal fluid regions have the same intensity values independent of the orientation (*up-down*, *left-right*, and *front-back*) of the applied diffusion gradient



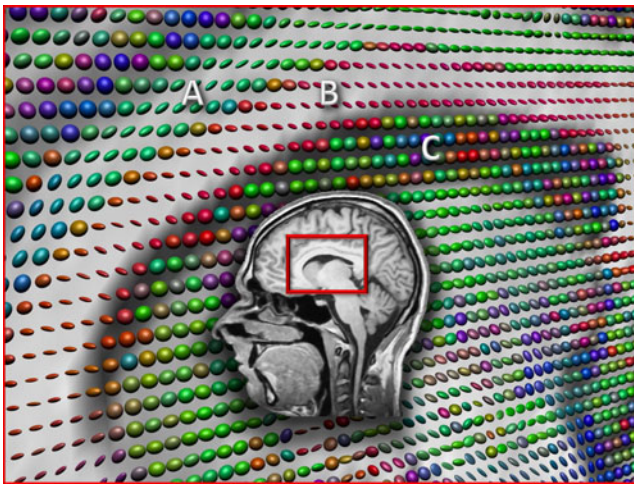


Fig. 3 Geometric representation of a diffusion tensor “image”. In contrast to a scalar image, where each voxel consists of one intensity value (e.g., such as for the sagittal T1-weighted map shown in the middle of the image), a diffusion tensor image has six numbers per voxel that describe the shape and orientation of an ellipsoid. In this figure, ellipsoids are shown for only one sagittal slice, as indicated by the *red rectangle*, and overlaid by the T1-weighted image for anatomical reference. Noteworthy is that the shape and color of these ellipsoids are not random, but that they can reflect the coherence and orientation of the underlying white matter pathways (*red* = left-right; *green* = front-back; *blue* = up-down). While being homogeneous on the T1 image, the regions indicated by “A” and “B” clearly show different diffusion orientations, reflecting the orientations of the cingulum and corpus callosum pathways, respectively. The ellipsoids in region “C” are less pointy and represent isotropic diffusion voxels in cerebrospinal fluid regions. Notice that the main orientation of the spherical ellipsoids (defining the color) is poorly estimated as can be appreciated by their random colors

the FA in well-organized WM bundles, such as the corpus callosum, will be closer to one. In the FA-map, (an image where the intensity reflects the FA-value in that voxel), we therefore see the CSF appearing dark and the WM bundles bright. An overview of these parametric maps is shown in Fig. 4(a)–(d).

The principal eigenvector, which is associated with the principal (i.e., largest) eigenvalue, represents the orientation where the diffusion is maximal and is often assumed to correspond with the orientation of the underlying WM fiber pathways. By adding color-coded information about this dominant diffusion orientation to the FA map we can obtain the widely used directionally encoded color (DEC) map (Pajevic and Pierpaoli 1999) (see Fig. 4(e)–(f)). In doing so, microstructural tissue coherence can now be visualized in combination with the dominant diffusion orientation (red = left-right; green = front-back; and blue = up-down). For example, parts of the corticospinal tract going in the up-downwards direction are visualized in blue, whereas parts of the corpus callosum with a left-right orientation are shown in red.

Relating microstructural properties to diffusion parameters

In the human CNS, neurons are the cells that transmit nerve impulses from one part of the brain to another. They are composed of dendrites, receiving the signal at the synapses, and of axons, guiding the signal through the neuron. Inside the axon, cylindrical microtubules and neurofilaments are inter-connected through small microfilaments, forming a dense cytoskeleton. The axon is surrounded by the axonal membrane and wrapped in layers of fatty myelinated oligodendrocytes, called myelin sheaths. A tissue called endoneurium keeps groups of axons together, forming fasciculi. These, in turn, are bundled in nerve fibers and provided nutrients by blood vessels. Given this complex and multi-layer structure, it is clear that the physical interpretation of diffusion parameter changes is not straightforward. Non-random motion of water particles could be affected by any of the nerve fiber’s constituents and could modulate the diffusion signal accordingly. However, *in vitro* and *in vivo* experiments have shown that the influences of axonal transport, the axonal cytoskeleton, or local gradients introduced by differences in susceptibility on the observed signal are negligible (Lian et al. 1994; Trudeau et al. 1995; Beaulieu and Allen 1996).

Apart from neurons, white matter consists of glial cells, which make up the largest part of the CNS. They act as supporting structure for the neurons and are amongst others

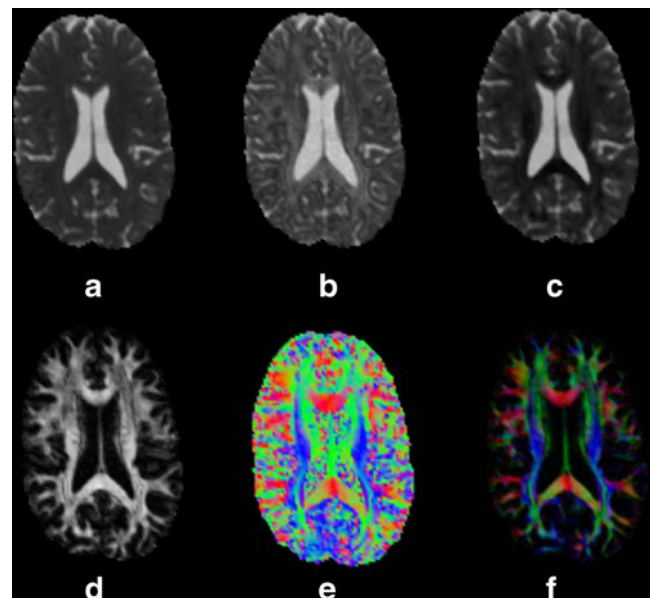


Fig. 4 Diffusion tensor imaging parameter maps: **a**, **b**, and **c** are the mean, axial, and radial diffusivity, respectively; **d** is the fractional anisotropy; **e** is the color information derived from the first eigenvector (*red* = left-right; *green* = front-back; *blue* = up-down); and **f** is the directionally encoded color map, which is constructed by combining image maps **d** and **e**

important for homeostasis. Oligodendrocytes, responsible for producing the myelin sheaths, were mentioned above. Yet, other glial cell types may be involved in anisotropy as well. Astrocytes, being the most abundant glial cells, have a stellate morphology, which makes them macroscopically isotropic. This is why it is currently believed that they would either not affect anisotropy, or reduce it. However, in some cases anisotropy was found to increase because of asymmetrical extension of glial processes in the direction of the lesion following traumatic brain injury (Mansour et al. 1990; Oberheim et al. 2008) or due to the coherent rearrangement of astrocytes also following injury (Budde et al. 2011). White matter anisotropy was also found to increase with an increase in astrocyte concentration after a learning task (Blumenfeld-Katzir et al. 2011). This indicates a link between neuroplasticity (in terms of astrocyte shape change and increase of processes) and diffusion estimates. It is known that astrocytes exist in two shapes: protoplasmic and fibrous astrocytes. The latter are most common in white matter, have intrinsically longer processes, and in the normal brain they are aligned parallel to white matter fibers. Glial cells may thus have an influence on DTI estimates. However, it is generally assumed that the main contributors to FA are the axonal membrane and the myelin sheath around the axons (Beaulieu and Allen 1994b). For more details on contributing factors of anisotropy we refer to a comprehensive review paper of Beaulieu (Beaulieu 2002).

Various WM disorders that may affect the axonal membrane and the myelin sheath have been associated with increased or decreased anisotropy measures. Reduced FA values, for instance, were found in cases of demyelination (Lopes et al. 2012) (Hanyu et al. 1999; Zhang et al. 2012), edema (Ling et al. 2012; Wright et al. 2012), gliosis (Budde et al. 2011), inflammation (Lodygensky et al. 2010; Looij et al. 2012) increased axon diameter (Takahashi et al. 2002), lower axonal packing density (Takahashi et al. 2002), tortuosity (Takahashi et al.

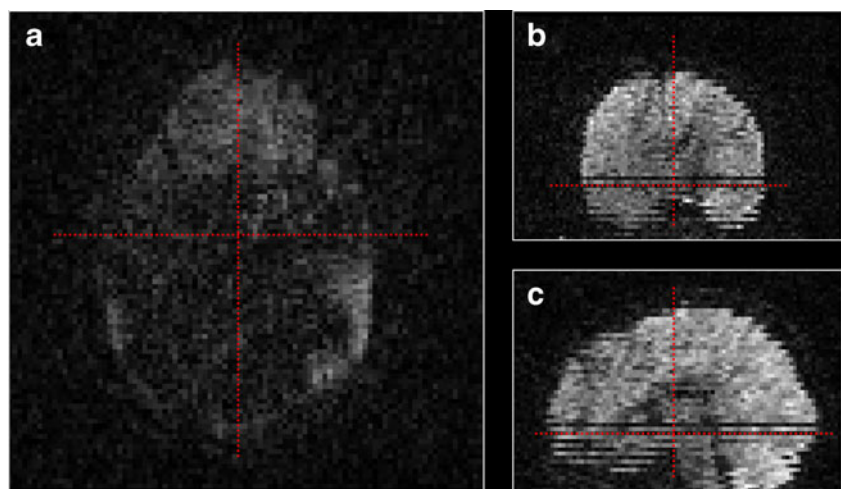
2000), and increased membrane permeability (Beaulieu and Allen 1994a). Similar relationships were made for the other diffusion parameters. In particular, an increased RD was found in the case of a decrease in myelin thickness (Song et al. 2002, 2005; Thomalla et al. 2004) and a reduced AD in the case of axonal loss (Song et al. 2002). Important to note is that all of these findings represent one-way conclusions: a known change in composition, size, and structure of axonal membrane and myelin sheath typically results in diffusion parameter changes. Conversely, drawing solid conclusions about pathophysiology from the estimated diffusion parameters is quite difficult (see also section “[Considerations on diffusion tensor imaging](#)”).

Preprocessing

Before starting a DTI analysis, there are several preprocessing steps that require attention and can be summarized as follows:

- 1) As with any measurements, data quality assessment (QA) is recommended and can consist of looping through the DW-MR images at different views (in the coronal, sagittal, and axial image plane). In doing so, images with gross image distortions, such as large signal dropouts and interleave artifacts (e.g., Fig. 5), which would corrupt further analysis, can be easily identified and excluded (Jones and Leemans 2011; Tournier et al. 2011).
- 2) Typically, with acquisition times ranging in the order of 5 to 20 min, subjects will have moved slightly (subject motion can easily be seen by flicking quickly between the first and last DW-MRI image). This misalignment across the DW-MRI images is further pronounced by geometric distortions caused by eddy currents, which, in turn, originate from the rapid switching of magnetic

Fig. 5 An example of a severely corrupted axially acquired diffusion-weighted (DW) MR data set due to subject motion. The axial image **a** shows signal ‘dropouts’, i.e. loss of signal, which can be spotted easily as *dark lines* in the coronal (**b**) and sagittal (**c**) orientations



gradients. The adverse effect of eddy currents can be reduced by collecting additional information during the acquisition phase, and/or by registration approaches (Andersson and Skare 2002). An important consideration is that the orientation information of the applied diffusion gradients, which is contained in the b-matrix, should also be rotated when the DW-MRI images are realigned as part of the registration procedure (Leemans and Jones 2009). Neglecting this latter step will introduce systematic deviations in the diffusion measures. Figure 6 shows an example of the DEC map before (a) and after (b) correcting for subject motion and eddy current induced geometric distortions.

- 3) To reduce scan time, Echo Planar Imaging (EPI) is commonly used for acquiring the individual DWIs (Turner and Lebihan 1990). EPI is a fast acquisition scheme, which reduces motion sensitiveness while having an excellent signal to noise ratio (SNR). The drawback is that it is prone to geometric and intensity distortions caused by field inhomogeneities (Jezzard and Balaban 1995; Du et al. 2002). Especially if fiber tractography (FT—see “Analysis” section) is going to be used, correcting for this artifact will significantly improve subsequent analyses (Fig. 7) (Kybic et al. 2000; Wu et al. 2008; Tao et al. 2009; Irfanoglu et al. 2012).
- 4) Once the DW-MRI images are corrected for subject motion, susceptibility artifacts, and eddy current induced distortions, the diffusion tensor can be estimated in each voxel. Different algorithms exist for this fitting procedure, such as ordinary least squares (OLS), weighted linear least squares (WLLS), and nonlinear

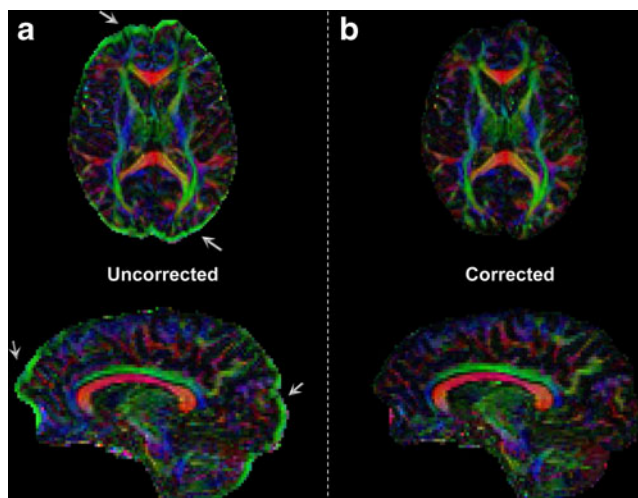


Fig. 6 In **a** and **b**, directionally encoded fractional anisotropy maps are shown before and after correcting for subject motion and eddy current induced geometric distortions. The bright rims at the *top/bottom* of the images indicated in **a**, which indicate the presence of these artifacts, are no longer visible after the correction procedure as shown in **b**

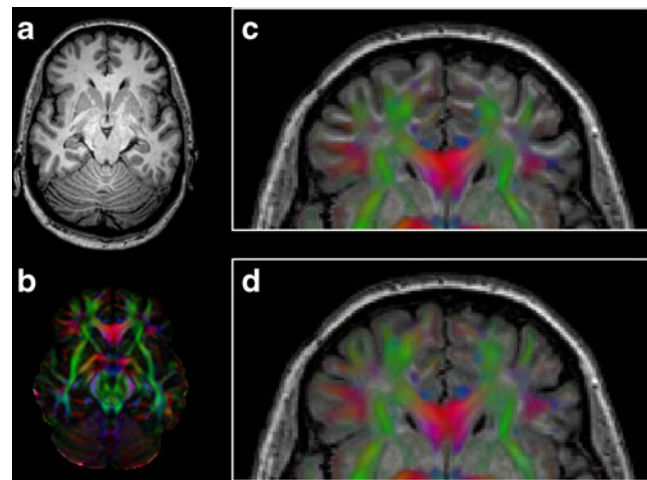


Fig. 7 By combining an undistorted structural T1-weighted MR image (**a**) with the directionally encoded fractional anisotropy map of the same subject (**b**), one can appreciate the presence of EPI related geometric distortions from the overlay in **c**. The alignment between these images is clearly improved after correcting the DTI data for this artifact, as shown in **d**

least squares (NLLS) (Jones 2004; Veraart et al. 2012). Data outliers (e.g., signal dropouts due to physiological noise, such as cardiac pulsation, swallowing, respiratory motion, etc.), however, will have an adverse impact on the diffusion parameter estimations if not accounted for (Fig. 8). Various methods exist to detect and remove such outliers and are recommended for quantitative analyses (Mangin et al. 2002; Chang et al. 2005, 2012).

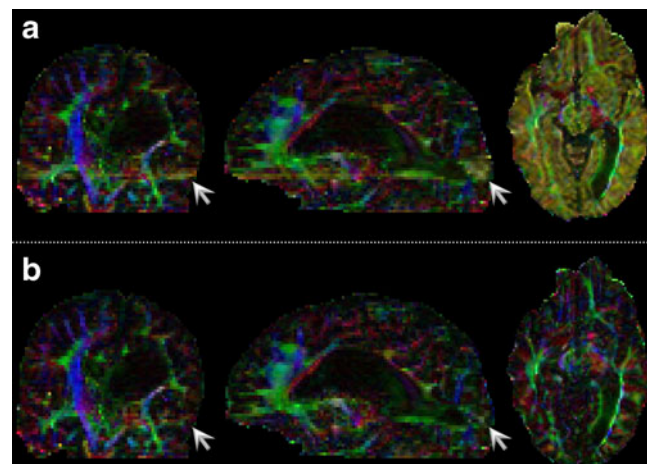


Fig. 8 From *left to right*: coronal, sagittal, and axial directionally color encoded fractional anisotropy maps of a subject with an abnormally large cerebrospinal fluid cavity. In **a**, these maps were calculated with a linear least squares estimation—i.e., the procedure typically provided by the major MR vendors—which is sensitive to data artifacts (see *arrows*). The maps in **b**, on the other hand, were computed using a robust diffusion tensor estimation approach, called RESTORE (Chang et al. 2005). Being less sensitive to corrupted diffusion signals, RESTORE produces more accurate diffusion maps

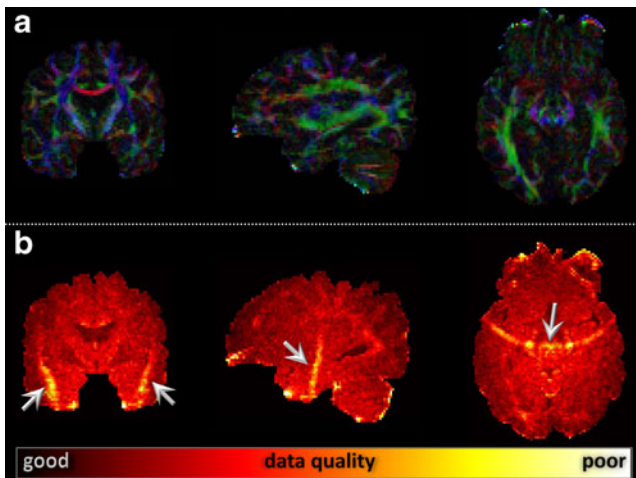


Fig. 9 In **a**, coronal, sagittal, and axial directionally color encoded fractional anisotropy (FA) maps are shown. For each of these maps, the associated average of the absolute differences between the measured and the fitted signals (i.e., the “residual” map) is displayed in **b**. This residual map is a sensitive way to identify artifactual signal intensities with high values suggesting a poorer quality. Notice, for instance, that while “ghosting” (e.g., due to insufficient fat suppression) can easily be seen on the residual map (see *arrows* in **b**), it is difficult to spot this artifact on the color encoded FA maps shown in **a**

- 5) The importance of QA cannot be stressed enough. An important final step is to look at the residuals of the tensor-fitting procedure (Tournier et al. 2011). A “residual” map indicates for every voxel how well the diffusion tensor model fits the acquired data. Ideally, residuals should be low and similar throughout the image volume. The residual map can reveal artifacts that are not always visible on the FA map or the individual DWIs and can be used as an efficient tool to provide feedback to the MR

physicists or engineers that design and optimize the acquisition sequences (Fig. 9).

With the diffusion tensor fitted in every voxel it is now possible to obtain the desired parameter maps, such as the FA, MD, RD, and AD, which can then be used for further analysis.

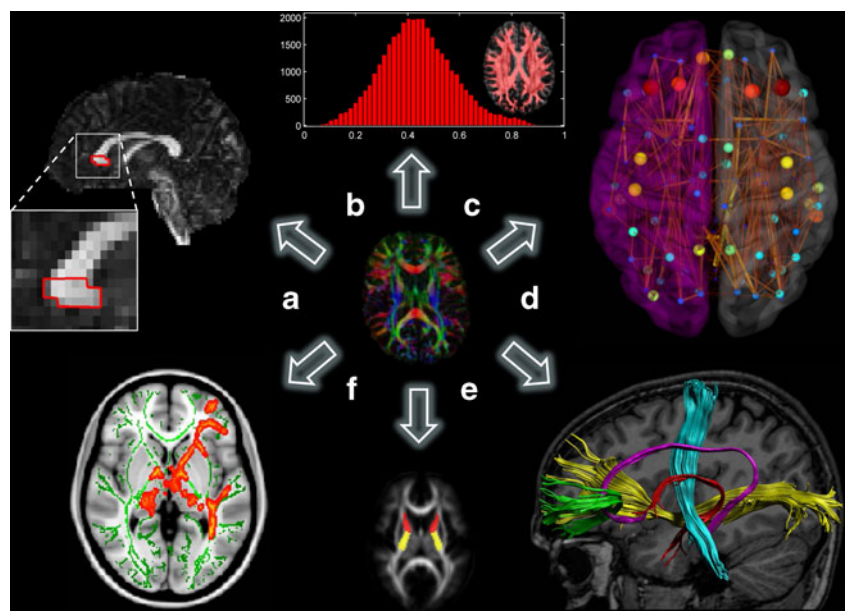
Analysis

There are several ways to analyze DTI data, each having its own specific benefits and drawbacks, which, in combination with the research question, will guide the user in their choice. In the following paragraphs, a brief overview is given of the most common approaches, which make use of (i) regions-of-interest; (ii) histograms; (iii) fiber tractography; (iv) atlas labels; (v) voxel based analysis; or (vi) graph theory of networks (Fig. 10).

Region-of-interest (ROI) analysis

If one is interested in investigating a specific WM fiber bundle, such as, for instance, the splenium of the corpus callosum (CC), drawing a “region-of-interest (ROI)” around this WM structure on a DTI parameter map (e.g., the FA, MD, etc.) is the most common and straightforward way of obtaining the underlying data values, which can then be used for further descriptive statistics (e.g., (Snook et al. 2005)). Being very time-consuming, this approach may not be feasible for large cohorts. In addition, drawing multiple ROIs on 2D image planes to indicate a 3D obliquely oriented WM structure (e.g., the uncinate fasciculus) requires the necessary anatomical expertise and experience.

Fig. 10 A schematic overview of the most common approaches for analyzing DTI data sets: **a** drawing regions-of-interest (ROIs); **b** histogram based analysis; **c** graph theoretical network analysis; **d** fiber tractography; **e** atlas based analysis; and **f** voxel based analysis



Consequently, the results can be variable across different raters.

Histogram analysis

When dealing with diseases that may induce a global diffuse effect on DTI estimates, a histogram-based analysis may be preferred. Several properties of the histogram (e.g., peak location, modus, median, kurtosis, inter-quartile range, etc.) are then typically derived and used for further inference (e.g., (Cercignani et al. 2000)). While being sensitive and fully automated, this approach cannot provide any specificity in terms of location where the effect/pathology is taking place. In addition, histogram based analyses may suffer from the inclusion of voxels that were not classified correctly in a prior segmentation step (e.g., during CSF or background masking).

Fiber tractography (FT) analysis

Fiber tractography (FT)—also known as fiber tracking or tract tracing—refers to the in vivo virtual reconstruction of WM pathways based on the underlying diffusion orientation information (for a recent overview, see (Lazar 2010)). By constraining pathways (not) to pass through predefined regions (Conturo et al. 1999) and by integrating the DTI measures associated with these fiber trajectories, one can obtain more anatomically specific diffusion estimates than with the conventional ROI based approach. The major disadvantage, however, is that high-SNR DW-MRI data is needed in order to minimize the error accumulation that exists during tract propagation (Lazar and Alexander 2003).

In general, FT can be categorized into “deterministic” and “probabilistic” methods. The deterministic FT approaches can be characterized as follows. From a specified position, coined a “seed” point, a single tract pathway is generated by consecutively following the local fiber orientation estimates—quite similar to reconstructing “streamlines” from a velocity field in fluid dynamics. Important to realize is that with deterministic FT there is no information about the reliability of the reconstructed pathway (Alexander 2010). By contrast, with probabilistic FT approaches, multiple pathways are typically launched from a single seed point providing a means to quantify the uncertainty related to the fiber trajectories. More specifically, for each pathway “realization” and at each position along the trajectory, the uncertainty of the orientation estimate (Jones 2003; Jones and Pierpaoli 2005) is taken into account (Behrens et al. 2007; Berman et al. 2008; Jones 2008; Descoteaux et al. 2009; Haroon et al. 2009; Jeurissen et al. 2011). The resulting distribution of pathways provides a degree of dispersion or precision when propagating through the data. It should be clear that probabilistic FT results merely reflect the likelihood that pathways will end up in a particular brain region when starting from a specified seed point (Jones

2010a). Also noteworthy is that most probabilistic FT methods are based on their deterministic FT counterparts and, hence, suffer from the same limitations (Parker 2010).

Atlas based analysis

By using pre-parcellated WM regions, defined on some template of interest, one can use registration tools to automatically transform these atlas labels to each individual subject and then calculate DTI measures of interest at the corresponding locations (e.g., Mori et al. 2008). Being objective and reproducible, it overcomes many of the limitations that accompany the manual ROI based analysis. Inter-individual differences, the choice of template, and the type of pathology, however, may affect the reliability of the coregistration accuracy (Verhoeven et al. 2010; Oishi et al. 2011).

Voxel based analysis (VBA)

If there is no prior knowledge or hypothesis about the extent or location of the pathology, using pre-defined ROIs may not be appropriate. For instance, the effect of chemotherapy on WM may not necessarily be confined to predefined ROIs. In this situation, voxel based analysis (VBA) can be an initial exploratory tool for detecting potential group differences. With VBA all subjects are first transformed to a common template space such that spatial correspondence of the same anatomical structure across subjects is achieved. Subsequently, statistical tests related to diffusion measures, such as FA, MD, etc. can be performed for each voxel. Despite being fully-automated, VBA requires good alignment of brain tissue between subjects, which may not always be the case. In an attempt to improve the reliability of VBA, “tract based spatial statistics” (TBSS) was proposed (Smith et al. 2006). While TBSS may reduce the likelihood of artifactual findings and can be considered to be the most popular VBA approach to date, it has several shortcomings of its own as discussed elsewhere (Jones and Cercignani 2010; Van Hecke et al. 2010a; Edden and Jones 2011; Preti et al. 2011). In any case, using advanced coregistration techniques (Park et al. 2003; Van Hecke et al. 2007) and population-specific DTI based templates (Jones et al. 2002; Van Hecke et al. 2008b, 2011) are recommended to improve the reliability of VBA results.

Graph theoretical network analysis

With graph theory, the brain can be represented in an abstract way as a set of “nodes”, defined by anatomical regions in the cortex, and “edges”, which reflect structural connection properties between these nodes (e.g., (Hagmann et al. 2008)). Using FT methods to define the node/edge characteristics, which are typically represented by “connectivity matrices”, such a graph theoretical analysis (GTA) provides a novel way

to explore topological and geometrical properties of brain networks, such as clustering coefficient, small worldness, efficiency, path length, connectivity degree, among others (for an in-depth discussion of these measures, see (Rubinov and Sporns 2010)). As with functional MRI based GTAs (e.g., (Caeyenberghs et al. 2012b)), it is believed that diffusion MRI based GTAs will become an effective and informative way to investigate structural brain properties in health (Li et al. 2009) and disease (Caeyenberghs et al. 2012a, b; Reijmer et al. 2013).

DTI in non-CNS cancer patients and survivors

To date, only a few studies have used DTI to investigate possible chemotherapy-induced WM changes in patients with non-CNS cancer. Using PUBMED, we found four studies that used DTI in groups of patients with breast cancer (Abraham et al. 2008; de Ruiter et al. 2011a; Deprez et al. 2011, 2012)

(Table 1). The only other non-CNS cancer group where DTI was used to study potential therapy-induced changes, was in long-term survivors of childhood Acute Lymphoblastic Leukemia (ALL) (Khong et al. 2006; Dellani et al. 2008; Porto et al. 2008; Aukema et al. 2009; Schuitema et al. 2012). ALL survivors were treated during childhood with prophylactic whole-brain radiation and/or intrathecal chemotherapy to bypass the blood brain barrier. As this special issue of Brain Imaging and Behavior is dedicated to the cognitive effects of cancer and cancer therapy not targeted to the brain in non-CNS cancers patients, we considered ALL studies beyond the scope of this review article. We will, however, list these ALL DTI studies in Table 2 for the interested reader. All studies listed in Tables 1 and 2, consistently report changes in DTI-parameters after cancer treatment, reflecting associated microstructural WM alterations due to this treatment. In the following sections we will summarize the main findings resulting from the cross-sectional and longitudinal DTI

Table 1 DTI studies in patients with breast cancer and survivors

Study	Subjects # (mean age)	Assessment	DTI-acquisition parameters	DTI-analysis method	Main findings
Abraham et al (2008)	10 SD C+ (49y) 9 HC (46y)	Cross- sectional 22 months after CT	3T b-value= 1,000 s/mm ² # directions=25	FA ROI analysis in genu and splenium of CC	- C+ has lower FA in genu of CC then HC - Sign correlation between FA and processing speed in genu of CC
Deprez et al. (2011)	17 SD C+ (45y) 18 HC (45y) 10 C- (43y)	Cross- sectional 4,3 months after CT	3T b-value=800 s/ mm ² # directions=45	FA, MD SPM whole brain voxel-based analysis	- C+ has lower FA and higher MD in frontal and temporal WM then HC and C- including superior and inferior longitudinal fasciculus, fronto-occipital fasciculus, CC, cingulum, ALIC and corona radiata - Sign correlations between FA and cognitive functioning in WM tracts known to be involved in cognition
de Ruiter et al. (2011a)	17 HD C+ (56y) 15 C- (58y)	Cross- sectional >9 years after CT	3T b-value= 1,000 s/mm ² # directions=32	FA, MD TBSS Tract-based spatial analysis	- C+ has lower FA and higher MD in anterior and posterior parts of the brain including inferior and superior longitudinal fasciculus, fronto-occipital fasciculus, CC, internal and external capsula, posterior thalamic radiation and corona radiata - Differences in DTI parameters are co- localized with differences in fMRI activa- tions in C+ - Sign correlation of DTI parameters and 1H- MRS NAA/Cr and NAA in C+
Deprez et al. (2012)	34 SD C+ (44y) 19 HC (44y) 16 C- (43y)	Longitudinal Baseline: before CT 4 months after CT	3T b-value=800 s/ mm ² # directions=45	FA SPM whole brain voxel-based analysis Population-based atlas	- C+ has sign decreased FA after CT when compared to baseline in frontal, parietal and occipital WM including superior longitudinal fasciculus, CC and corona radiata - No sign changes in FA for C- and HC - Sign correlation between decrease in FA and decrease in cognitive performance in C+

SD C+ patients treated with standard dose chemotherapy; *HD* C+ patients treated with high dose chemotherapy; *C-* patients not treated with chemotherapy; *HC* healthy controls; *FA* fractional anisotropy; *MD* mean diffusivity; *CC* corpus callosum; *CT* chemotherapy; *ALIC* anterior limb internal capsula

studies done in breast cancer patients and provide additional perspectives on the reported findings.

ROI-based cross-sectional DTI study in breast cancer patients

Abraham and coworkers (Abraham et al. 2008) were the first to use DTI to investigate the effect of adjuvant chemotherapy on normal-appearing WM in women with breast cancer. In a pilot study, they investigated the FA in the genu and the splenium of the CC in 9 healthy controls and 10 breast cancer survivors almost 2 years after treatment with doxorubicin-cyclophosphamide with/without taxane. They included patients that reported to have experienced cognitive change after chemotherapy. In this cross-sectional ROI-based study, the CC was selected, as this is the largest WM bundle and known to be

vulnerable to neurotoxicity from alcohol and solvents (Haut et al. 2006; Pfefferbaum et al. 2010). They reported significant lower FA in breast cancer survivors in the genu of the CC, but not in the splenium when compared to healthy controls. Interestingly, this lower FA in the cancer survivors could be linked with slower processing speed. The results of this pilot study suggest that adjuvant chemotherapy affects WM in the genu of the CC and that this is related to the cognitive deficits experienced by patients.

Whole brain cross-sectional DTI studies in breast cancer patients and survivors

The pilot study by Abraham et al. (Abraham et al. 2008) was an ROI-based study and was limited to the analysis of WM in the CC only. By contrast, DTI studies by (Deprez et al.

Table 2 DTI studies in Acute Lymphoblastic Leukemia (ALL) survivors

Study	Subjects # (mean age)	Assessment	DTI-acquisition parameters	DTI-analysis method	Main findings
Khong et al. (2006)	9 IC + (13.1y) 9 CRT + IC+ (14.8) 9 MED CRT + IC + (11.8y) 55 HC (12.1)	Cross-sectional 5 years after CT	1.5T b-value=1,200 s/mm ² # directions=25	FA ΔFA%	- ΔFA% was significantly related to IQ after adjusting for effects of age at treatment, radiation dose and time interval since treatment
Porto et al. (2008)	10 IC + (23y) 10 CRT + IC + (14.8y) 21 HC	Cross-sectional 15 years after CT	3T b-value=700 s/mm ² # directions=6	FA SPM whole brain voxel-based analysis	- CRT + IC + had lower FA then HC in WM bordering caudate nuclei - IC + group showed trend for lower FA then HC
Dellani et al. (2008)	13 CRT + IC + (17–37y) 14 HC (22–40y)	Cross-sectional 16–28 years after CT	1.5T b-value=1,000 s/mm ² # directions=6	FA MD ROI analysis	- CRT + IC + had lower FA then HC in temporal WM, hippocampi and thalami - CRT + IC + had higher MD then HC in temporal WM
Aukema et al. (2009)	6 MED CRT + IC + (13.6y) 5 HD IC + (15.5y) 5 SD IC + (13.2y) 17 HC (13.9y)	Cross-sectional At least 3 years after CT	3T b-value=1,000 s/mm ² # directions=32	FA ROI analysis	- Patients had lower FA then HC in right inferior fronto-occipital fasciculus (IFO) and in the genu of the CC - Significant correlation between processing speed and FA in splenium and body of CC - Significant correlation between motor speed and FA in IFO
Schuitema et al. (2012)	24 CRT + IC (31.9y) 29 IC (24.5y) 49 HC (26.5y) 20 HD CT (29.9y)	Cross-sectional 25 years after treatment	1.5T b-value=700 s/mm ² # directions=60	FA SPM whole brain voxel-based analysis	- CRT + IC group had significantly decreased FA vs HC in CC, cingulum, orbitofrontal WM - Trends for lower FA in CT only groups vs HC - Decreased FA correlated with impaired cognitive performance - Stronger decline of FA with age in CRT+ CT group then controls

CT chemotherapy; MED CRT + IC+ survivors of childhood medulloblastoma treated with cranial radiotherapy AND intrathecal CT; HC healthy controls; CRT + IC+ ALL survivors treated with cranial radiotherapy AND intrathecal CT; y years; IC+ ALL survivors treated with intrathecal CT; SD standard dose chemotherapy; HD high dose chemotherapy; CC corpus callosum; MD mean diffusivity; FA fractional anisotropy; ΔFA% percentage difference in mean whole brain WM FA for each patient compared with the age-matched control group

2011) and (de Ruiter et al. 2011a) investigated possible chemotherapy-induced WM changes throughout the entire brain. The cross-sectional study by Deprez et al. used an SPM whole-brain VBA in combination with detailed cognitive assessment to study 17 patients with breast cancer who were treated with fluorouracil (5-FU), epirubicin and cyclophosphamide (FEC) with/without taxane about 4 months after chemotherapy. Lower FA and higher MD were observed in chemotherapy-exposed patients when compared to healthy controls ($n=18$) and non-exposed patients ($n=10$) in frontal and temporal WM. These differences were found in WM tracts known to be involved in cognitive functioning like the superior and inferior longitudinal fasciculus, fronto-occipital fasciculus, CC and cingulum. Interestingly, in an explorative analysis, Deprez et al. found that the affected WM areas were more extended in the patient group that was cognitively impaired when compared to the cognitively unimpaired group. Cognitive impairment was defined as having at least two neuropsychological test scores outside normal variance. In concordance with the pilot study of Abraham et al., Deprez et al. found a link between abnormal diffusion properties and cognitive impairment. They reported significant correlations of FA with neuropsychological tests covering the domain of attention and processing speed in temporal and parietal WM tracts, including the superior and inferior longitudinal fasciculus. Also subjective self-reported cognitive complaints correlated well with FA in frontal and parietal WM regions.

De Ruiter and coworkers conducted another cross-sectional study comparing 17 breast cancer survivors 10 years after treatment with adjuvant high-dose chemotherapy with 4 cycles standard-dose FEC and 1 cycle high-dose CTC (cyclophosphamide, thiotepa, carboplatin) combined with stem-cell transplantation to 15 non-chemotherapy exposed breast cancer survivors (de Ruiter et al. 2011a). In this multimodal study they combined results from DTI, single voxel proton MR spectroscopy (1H-MRS), and T1-weighted voxel-based morphometry (VBM) to investigate possible long-term brain injury 10 years after high-dose chemotherapy. They used TBSS to look at WM differences and reported decreased FA and increased MD in widespread anterior and posterior parts of the brain, also including inferior and superior longitudinal fasciculus, fronto-occipital fasciculus and CC (Fig. 11). These findings corroborate with studies of Abraham et al. (Abraham et al. 2008) and Deprez et al. (Deprez et al. 2011) who studied standard-dose treatment 4 months and 2 years after treatment, respectively. In contrast to these two studies, however, de Ruiter et al. did not find significant correlations between DTI parameters and cognitive test indices 10 years after treatment, only a marginally significant negative correlation between MD and the Flanker test was found (Eriksen and Eriksen 1974). Interestingly, the areas with changed WM

microstructure co-localized with areas with reduced gray matter volume and functional MRI (fMRI) hypoactivation (as reported in their previous publication (de Ruiter et al. 2011b)). Additionally, DTI parameters correlated negatively with 1H-MRS measures only in the chemotherapy-treated group, which they suggest could be linked to axonal damage in this group.

Therapy-induced myelin degeneration?

The observed changes in DTI parameters in the above studies might be related to demyelination of WM axons or axonal injury after chemotherapy. To gain a better understanding of the observed WM changes, both Deprez and de Ruiter also studied radial (RD) and axial (AD) diffusivity (de Ruiter et al. 2011a; Deprez et al. 2011). These directional diffusivities may yield important information about the underlying neuropathology of these differences in DTI parameters. Deprez et al. revealed significantly higher values of RD in the WM of chemotherapy-treated patients compared with controls, whereas no significant differences were found in AD. Also de Ruiter and coworkers reported regional RD increases for the patient group and no between-group differences in AD. This observed pattern in combination with decreased FA and increased MD may be related to the demyelination of WM axons (Song et al. 2002). However, as mentioned earlier, we need to be very careful when interpreting changes in DTI parameters in terms of biological changes. Nevertheless, other evidence points us also in the direction of demyelination after chemotherapy. In the studies of de Ruiter and Deprez, all patients received systemic treatment with the antimetabolite 5-FU (de Ruiter et al. 2011a; Deprez et al. 2011). Han et al. reported that systemic treatment with 5-FU in mice causes damage to myelinated WM tracts and deregulates Olig2 expression, which is crucial for generating functional oligodendrocytes (myelin-forming cells), leading to a syndrome of delayed myelin destruction in the CNS (Han et al. 2008). This delayed and extensive myelin damage was also detectable 6 months post treatment. When studied in vitro, non-dividing mature oligodendrocytes seem to be cell populations that are most vulnerable to the toxic effects of chemotherapeutic agents, even more vulnerable than cancer cells (Dietrich et al. 2006). Consistent with these in-vitro observations Dietrich and coworkers also observed increased cell death of oligodendrocytes after administration of an antimetabolite agent in animal models. The above findings from experimental research all point to myelin toxicity after chemotherapy. The interested reader is referred to excellent reviews on the cell-biological basis of chemotherapy-induced neurotoxicity by Seigers et al. (Seigers and Fardell 2011) and Dietrich et al. (Dietrich et al. 2008). Furthermore, Morelli et al. suggests that the cognitive impairment after

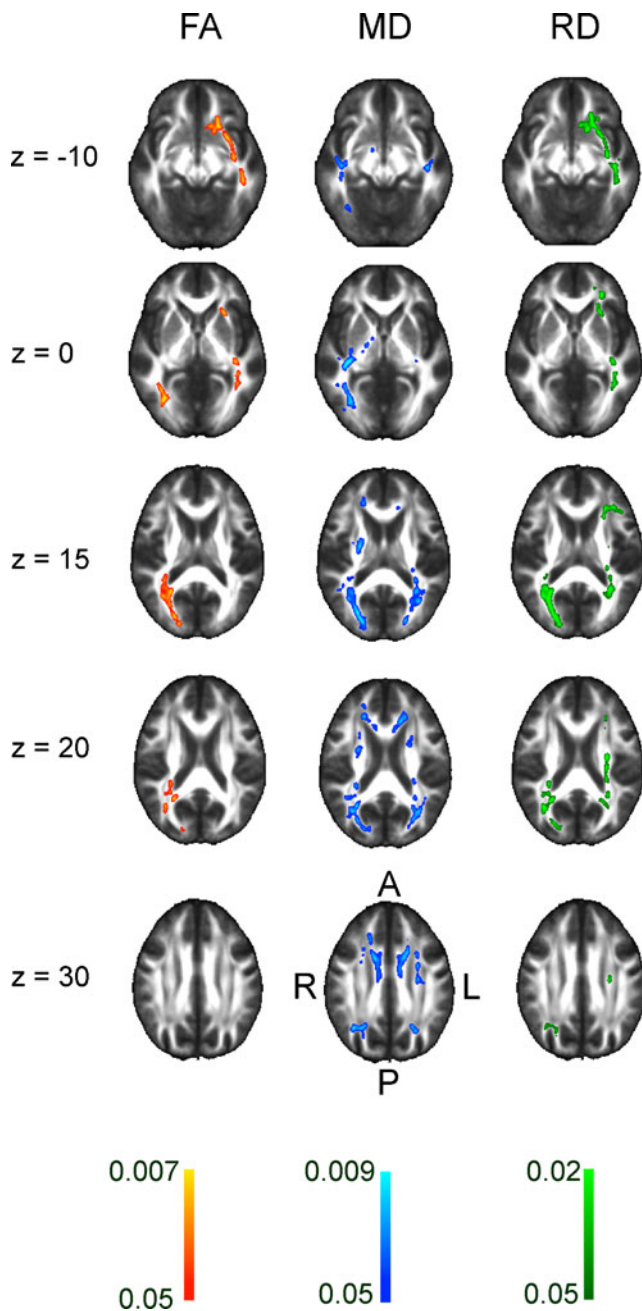


Fig. 11 Group differences in DTI values between the chemotherapy (CT) group and the no-CT group. DTI data were analyzed with tract-based spatial statistics (TBSS). Cluster-based thresholding at $P < 0.05$ was applied, fully corrected for multiple comparisons. Areas of the WM skeleton that show significant group differences are overlaid on the mean of the MNI normalized FA maps of all. Significant clusters have been thickened for ease of visualization. *Left panel* shows regions where the CT group has a lower FA than the no-CT group. *Middle panel* shows regions where the CT group has a higher mean diffusivity (MD) than the no-CT group. *Right panel* shows regions where the CT group has a higher radial diffusivity (RD) than the no-CT group. *Color bars* show range of corrected P values. (de Ruiter et al. 2011a; reprinted with permission from Human Brain Mapping, Volume 33, issue 10; Copyright 2011, with permission from John Wiley and Sons)

cancer therapy with antimetabolites (like 5-FU, methotrexate) could be a delayed consequence of defective myelin sheath production and that impairment of oxidative phosphorylation, which is essential for chemical energy production, is the ultimate cause of demyelination (Morelli et al. 2011). Also a postmortem examination of a 49-year-old female with chemotherapy-treated breast cancer demonstrated demyelination in several WM regions (Moore-Maxwell et al. 2004).

Whole brain longitudinal DTI study in patients with breast cancer

The previously described cross-sectional studies (Abraham et al. 2008; de Ruiter et al. 2011a; Deprez et al. 2011) are limited by the absence of a pretreatment baseline to which potential post-treatment changes can be compared. Several investigators have shown impaired cognitive functioning and functional imaging abnormalities already before the start of treatment in cancer patients (Wefel et al. 2004; Ahles et al. 2007; Quesnel et al. 2008; McDonald et al. 2010). Other factors than chemotherapy, e.g. the cancer disease process itself, could therefore also have contributed to the reported structural changes in WM. The purpose of the longitudinal DTI study of Deprez et al. was to study the whole-brain WM before and 3–4 months after completion of chemotherapy in a group of young women with breast cancer and evaluate potential changes in FA in combination with detailed cognitive assessment (Deprez et al. 2012). They compared 34 chemotherapy-exposed patients (FEC with/without taxane) to 16 non-chemotherapy-exposed breast cancer patients and 19 matched healthy controls. They found no baseline pretreatment differences between the 3 groups in FA values and cognitive testing (when controlling for differences in depression scores). After chemotherapy, however, FA values in frontal, parietal and occipital WM regions decreased when compared to baseline (Fig. 12), whereas no changes were observed in non-exposed patients or healthy controls within the same time-interval. While the two control groups improved their performance significantly in attention, memory and processing speed, probably because of practice effects, the patients treated with chemotherapy experienced cognitive decline in all three domains. This was accompanied with significantly increased self-reported cognitive complaints only in those women treated with chemotherapy. Furthermore, performance changes in attention and verbal memory correlated with mean regional FA changes in chemotherapy-treated patients. This suggests a link between longitudinal changes in cognitive functioning and changes in cerebral WM integrity in chemotherapy-exposed patients. The fact that no baseline differences were found between the groups and that WM changes were observed after treatment with

chemotherapy only, suggests that the detected changes in WM structure are specific to chemotherapy treatment, rather than solely reflecting cancer disease process or other cancer treatments.

Are some brain regions more vulnerable?

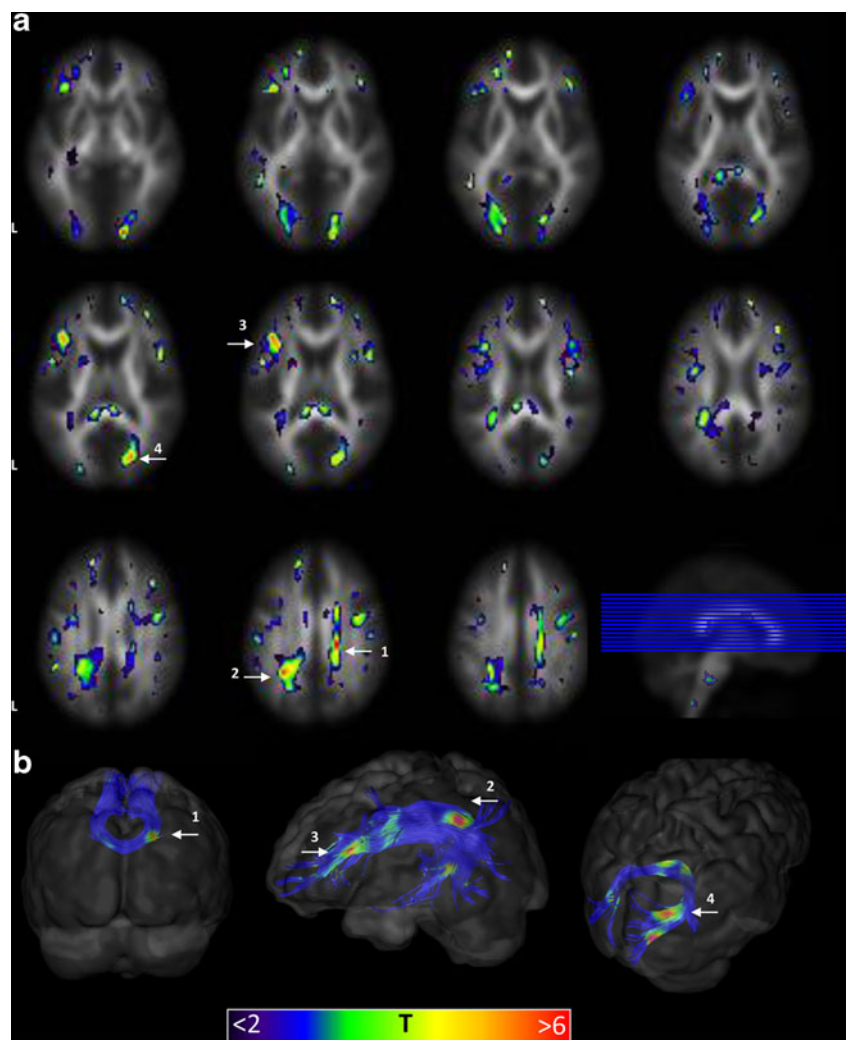
Taken together, the limited number of DTI studies done so far show a rather diffuse pattern of changes in DTI-parameters and related microstructural changes in WM. Decreased FA and increased MD have been reported in frontal, temporal, occipital and parietal brain regions. Interestingly, similarities can be seen in the WM tracts that have been reported across studies. All four DTI studies, investigating the impact of chemotherapy on WM microstructure, described alterations in the CC. Additionally, the three whole-brain VBA analyses showed alterations in the superior longitudinal fasciculus and the corona radiata. Furthermore, both cross-sectional VBA studies (de Ruiter et al. 2011a; Deprez et al. 2011) reported differences in the

inferior longitudinal and fronto-occipital fasciculus and the internal capsula. Other WM tracts that have been reported to be involved, but which are not overlapping across studies, include the external capsula, thalamic radiation (de Ruiter et al. 2011a) and cingulum (Deprez et al. 2011). Differences in the reported WM tracts across studies may be related to differences in chemotherapy regimen (high dose vs low dose), number of years after chemotherapy, the DTI acquisition sequence, DTI image processing techniques or study design (cross-sectional vs longitudinal).

More studies will be needed to investigate if one or more regions would be more vulnerable to chemotherapy-induced neurotoxicity than others. All four DTI studies reported WM alterations in the CC. It has been shown that the tightly packed fibers of the CC are particularly susceptible to toxic effects of for example alcohol (Pfefferbaum et al. 2006, 2009, 2010; Konrad et al. 2012), similarly this WM bundle could be more susceptible for chemotherapy-induced neurotoxicity.

Additionally, also changes in frontal WM have been consistently reported in the four DTI studies investigating

Fig. 12 Regions showing significantly decreased fractional anisotropy in chemotherapy-treated patients at 3 to 4 months after treatment (t2) when compared with baseline (t1, i.e., before treatment). **a** t-map (providing the t statistic in each voxel) overlaid on axial slices of the mean fractional anisotropy map from the whole group. **b** t-map overlaid on reconstructed WM tracts for a representative patient in the corpus callosum, superior longitudinal fasciculus, and for-cereps major. The white arrows indicate the reported regions significant at $P < .05$ familywise error corrected for multiple comparisons: 1, cluster covering parietal part of corona radiata, corpus callosum; 2, cluster covering parietal part of superior longitudinal fasciculus; 3, cluster covering frontal part of superior longitudinal fasciculus; 4, cluster covering part of for-cereps major. (Deprez et al. 2012; reprinted with permission from Journal of Clinical Oncology, Volume 30, issue 3; Copyright 2012, with permission from American Society of Clinical Oncology)



chemotherapy-induced neurotoxicity. A hypothesis called retrogenesis suggests that the latest myelinated regions, including the frontal regions and more posterior sites (e.g. occipito-temporal bounding), would be more vulnerable to aging processes and that degeneration therefore occurs in the reverse pattern of myelogenesis (Reisberg et al. 1999), the so-called anterior-posterior gradient. Late-myelinating fiber pathways include for example the inferior and superior longitudinal fasciculus. These long-association tracts, integrating frontal, parietal, occipital and temporal association cortices, play an important role in cognitive functioning (Karlsgodt et al. 2008; Turken et al. 2008; Van Hecke et al. 2010). An assumption is that oligodendrocytes of associative WM pathways are the most metabolically active cells and thus correspondingly vulnerable to the accumulation of metabolic damage (Madden et al. 2012). Many studies investigating DTI WM changes of aging report decreased FA and increased diffusivity with increasing adult age in frontal WM (Pfefferbaum et al. 2005; Salat et al. 2005; Sullivan and Pfefferbaum 2006; Bennett et al. 2010; Ziegler et al. 2010; Bartzokis et al. 2012). These changes in FA correlate well with changes in cognitive functioning. For example decreased cognitive processing speed, known to slow with age, correlates well with FA in CC, superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (IFOF) (Kerchner et al. 2012). If chemotherapy-induced neurotoxic changes in the brain would reflect a pattern of accelerated aging (Maccormick 2006; Edelstein et al. 2011) then according to this hypothesis the more frontal and long association fibers could be affected to a larger extent. This pattern of structural change in aging is consistent with the pattern of neuropsychological change that occurs in old age: memory impairment, slowing of processing speed, executive dysfunction, and attention difficulties (Madden et al. 2012). These are also the domains commonly found affected by cancer and its treatment.

Interestingly, similar patterns can be observed in WM changes and cognitive decline caused by other neurotoxic substances like industrial products (Haut et al. 2006; Kim et al. 2011), cocaine (Romero et al. 2010; Bell et al. 2011) or alcohol (Harris et al. 2008; Pfefferbaum et al. 2009; Schulte et al. 2012; Sorg et al. 2012). Also in these studies, neurotoxic-induced alterations in WM microstructure could be observed in frontal WM and/or long-association fibers. A study investigating work-related neurotoxic exposure in manganese-exposed welders reported microstructural alterations linked with subtle cognitive impairment in frontal WM (Kim et al. 2011). Also Lim et al. (Lim et al. 2008) described lower FA in cocaine users when compared to controls, specifically in inferior frontal white matter, while no FA differences were seen in other areas. Findings from Bartzokis et al. (Bartzokis et al. 2002) suggest that cocaine-dependence may arrest normal maturation of frontal WM in

addicted adults (age 19–45 years), which was not seen in a group of age-matched controls. Various DTI analyses in alcoholic patients demonstrated lower FA in frontal WM (Harris et al. 2008; Pfefferbaum et al. 2009; Sorg et al. 2012). Additionally, Pfefferbaum and coworkers showed that older alcoholic patients had greater WM structural deficits for their age than younger alcoholics (Pfefferbaum et al. 2006). Corroborating with these findings Boutros et al. (Boutros et al. 2000) described similarities in the disturbances in cortical information processing in alcoholism and aging, suggesting that alcohol neurotoxicity may accelerate the aging process. Taken together, these findings support the hypothesis that late-myelinating regions including the more frontal WM could be more vulnerable to neurotoxic effects and therefore could show effects of accelerated aging.

Interestingly, longitudinal VBM studies (McDonald et al. 2010, 2012b) demonstrated also reduced gray matter in frontal regions in chemotherapy-treated patients, while no changes were found in controls or patients who received hormone treatment but not chemotherapy. Similarly, studies looking at differences in brain activation between controls and patients that were treated with chemotherapy, reported altered brain activity in the frontal cortex. Silverman et al. (Silverman et al. 2007) reported 5–10 years after completion of chemotherapy, increased activation in the inferior frontal gyrus, using positron emission tomography (PET). These findings are in line with other functional MRI studies that also report differences in brain activation patterns after chemotherapy in the frontal cortex (de Ruiter et al. 2011b; Kesler et al. 2011; McDonald et al. 2012a).

Long term damage or recovery possible?

Whereas the study of de Ruiter et al. reported late effects (10 years) of high-dose adjuvant chemotherapy on WM microstructure in breast cancer survivors (de Ruiter et al. 2011a), the studies of Abraham and Deprez reported effects of standard-dose chemotherapy 2 years and 4 months after treatment, respectively (Abraham et al. 2008; Deprez et al. 2011). Whether standard-dose treatment has a similar detrimental effect on WM microstructure in the long run is still unknown. More research is needed to determine whether the detected chemotherapy-induced WM changes after standard-dose chemotherapy are reversible or whether there is long-term or even delayed WM damage. Animal studies describe delayed WM degeneration after treatment with 5-FU, suggesting worsening over time (Han et al. 2008). Plastic changes (e.g., increase in axonal thickness or myelin) under recovery, however, seem also plausible. First, several studies suggest that there could be (partial) recovery in damaged WM. Hua et al. (Hua et al. 2011) showed (partial) recovery of radiation therapy-induced WM changes in patients with brain tumors. Bell et al. (Bell et al. 2011)

reported WM changes that mark recovery from addiction as a function of abstinence duration in former cocaine-dependent individuals. Also Sidaros et al. (Sidaros et al. 2008) observed FA increases in WM tracts reflecting late recovery following traumatic brain injury.

Complementary to this, reorganization of existing intact WM tracts to (partially) take over functionality of damaged WM tracts could occur as well. For example, Thomas et al. (Thomas et al. 2005) demonstrated the reorganization of sensorimotor tracts in the unaffected side of spastic hemiparetic patients. In addition, from studies with healthy volunteers, we also know that training induces plasticity of WM microstructure, which is measurable with DTI. For example Takeuchi et al. (Takeuchi et al. 2010) showed that the amount of working memory training correlated with increased FA in WM regions that are thought to be critical in working memory. Additionally, Lövdén et al. (Lovden et al. 2010) showed that this experience-dependent plasticity of WM microstructure extends into old age. These findings suggest that WM microstructural properties can change in response to cognitive training and, therefore, suggest that cognitive training could also be an interesting therapeutic intervention for chemotherapy-induced cognitive impairment.

In summary, DTI-based assessment of the microstructural properties of WM may be sufficiently sensitive to investigate the neuronal substrate of chemotherapy-induced cognitive complaints. The cross-sectional and longitudinal DTI studies discussed in this review demonstrated WM impairment in important WM tracts involved in cognition in chemotherapy-treated patients compared with healthy controls and non-chemotherapy-treated patients, suggesting that there is a link between WM microstructural properties and chemotherapy-induced impaired cognition. Longitudinal changes in FA could therefore serve as a sensitive neuropathologic biomarker for treatment-induced neurotoxicity and follow-up on possible recovery.

Considerations on diffusion tensor imaging

Given its ease of use and its availability on most clinical MRI scanners, DTI is increasingly being used for investigating tissue characteristics in a wide range of clinical and biomedical applications, such as brain development (Huppi and Dubois 2006; Lebel et al. 2008; Verhoeven et al. 2010; De Bondt et al. 2012; Hemels et al. 2012), performance and learning (Moseley et al. 2002; Caeyenberghs et al. 2010b; Gooijers et al. 2011; Sisti et al. 2012; Zatorre et al. 2012), aging (Sullivan and Pfefferbaum 2006; Hsu et al. 2008, 2010; Van Hecke et al. 2008a), Parkinson's Disease (Van Camp et al. 2009; Sexton et al. 2011; Wang et al. 2012), peripheral nerves (Jambawalikar et al. 2010; van der Jagt et

al. 2012), depressive disorders (White et al. 2008; Carballedo et al. 2012; Emsell et al. 2012), autism (White et al. 2008; Langen et al. 2012; Verhoeven et al. 2012), stroke (O'Sullivan 2010; van der Aa et al. 2011), diabetes (Kodl et al. 2008; Hsu et al. 2012; Reijmer et al. 2012a), amyotrophic lateral sclerosis (Wang and Melhem 2005; Sage et al. 2009; Blain et al. 2011; van der Graaff et al. 2011), Alzheimer's Disease (Reijmer et al. 2012b), traumatic brain injury (Caeyenberghs et al. 2010a, 2011), multiple sclerosis (Rovaris and Filippi 2007; van Hecke et al. 2009a, 2010b), mild cognitive impairment (Cho et al. 2008; Parente et al. 2008) and neuroplasticity (De Groof et al. 2006, 2009; Zatorre et al. 2012). In most of these studies, measures derived from the diffusion tensor (typically, FA and MD) are compared between subject groups or correlated with other experimental variables of interest. While the analysis results may be genuine, that is, robust and reproducible, it is extremely difficult to draw any solid conclusions in terms of biophysical processes that underlie the observed findings. In the following sections, we discuss some fundamental principles of DTI to provide the reader with a better insight into the interpretation of analysis results and clarify common misconceptions that have originated from overenthusiastic claims that have appeared in recent literature.

What do we actually measure with DTI?

Roughly speaking, with conventional structural MRI the relaxation properties of induced tissue magnetization are characterized. In T2-weighted MRI, for instance, image contrast is generated by measuring the loss of coherence between proton spins. With diffusion-weighted (DW) MRI, an additional magnetic field gradient is applied along a particular axis making the proton spins *also* sensitive to diffusion along that orientation (Le Bihan et al. 1986). The diffusion (i.e., the random displacement of the protons due to thermal agitation) will cause an increase in phase dispersion and, hence, a signal loss. This signal decrease will be more pronounced at higher diffusion rates making the image appear darker. With DTI (Basser et al. 1994) we merely *measure* this signal attenuation along different (at least 6) diffusion-encoding gradient orientations—nothing else. After this data acquisition, the diffusion tensor is *estimated* from these DW signal amplitudes making it possible to calculate quantitative measures from the eigenvalues of the tensor (e.g., FA and MD) (Basser 1995; Basser and Pierpaoli 1996) or perform fiber tractography based on the first eigenvector of the tensor (Conturo et al. 1999; Jones et al. 1999b; Mori et al. 1999; Basser et al. 2000). So strictly speaking, we do not *measure* the diffusivity properties, but we *estimate* them by fitting the diffusion tensor to the signal measurements.

It is important to note that while the DW signal may be sensitive to several tissue properties (axonal density, degree of myelination, permeability of cell membranes), it is also sensitive to many other factors such as temperature, viscosity, and the presence of large macromolecules (Beaulieu 2002). In addition, the applied acquisition parameters (e.g., diffusion time, gradient strength/duration, voxel size, field strength, and number of gradient directions) and the choice of tensor estimation procedure can also affect the resulting diffusion values in a nontrivial way (Jones et al. 1999a; Jones 2004, 2010b; Jones and Basser 2004; Jones and Leemans 2011; Polders et al. 2011). Furthermore, the diffusion tensor is a model that approximates the underlying DW signal by assuming that the diffusion is Gaussian distributed (“hindered”). This assumption may not be generally valid as intra-axonal water compartments, among other factors, could induce a “restricted” diffusion component affecting the diffusion signal in a complicated manner. Given these concerns, it should be clear that DTI *cannot* provide direct measurements of *specific* microstructural tissue properties without any prior knowledge obtained from other experimental data or complementary information.

“Partial voluming” and “crossing fibers”

With typical voxel dimensions for clinical DTI studies ranging in the order of two to three mm, a mixture of multiple tissue types (e.g., any combination of gray matter (GM), WM, and/or CSF) may exist within a single voxel. For voxels that suffer from “partial voluming” (PV)—also known as “partial volume effect”, “powder averaging”, or “intra-voxel heterogeneity”—the observed diffusion signal is a combination of the signals associated with each tissue type (Frank 2001; Tuch et al. 2002). Parts at the edge of the fornix and the CC, for instance, are typically affected by PV, as voxels in these regions tend to show elevated diffusivity values due to the surrounding CSF (e.g., (Concha et al. 2005b)). By using fluid attenuated inversion recovery (FLAIR) based CSF suppression techniques (Papadakis et al. 2002) or post-processing methods (Metzler-Baddeley et al. 2012b), contamination from the free water component can be alleviated. In this context, other approaches have been developed to tackle CSF contaminated GM voxels in a similar way (Koo et al. 2009). Note that neglecting to correct for PV effects may bias analyses and complicate subsequent inferences (Concha et al. 2005a; Vos et al. 2011).

In voxels at the interface of two differently oriented WM fiber bundles (e.g., where the cingulum “brushes” the CC), a reduced FA value can be observed (Alexander et al. 2001). Such modulations in DTI measures are also present in voxels where fiber bundles bend sharply, merge, fan, and intersect with other WM pathways—a phenomenon that can

be described generically as the “crossing fibers” issue (Frank 2001; Tournier et al. 2011; Jeurissen et al. 2012). In “crossing fiber” regions, linking DTI findings with specific tissue properties is further complicated as the observed diffusion values may even vary purely based on changes in architectural configuration of the WM fiber pathways, irrespective of their underlying microstructural characteristics, such as degree of myelination or axonal density/packing/diameter distribution (Wheeler-Kingshott and Cercignani 2009; Caan et al. 2010; Vos et al. 2011, 2012).

Being a Gaussian model (think of the “ellipsoid” representation shown in Fig. 3), only one dominant diffusion orientation (i.e., the first eigenvector) can be determined from the diffusion tensor. For voxels with multiple fiber populations, the diffusion tensor will be estimated unreliably and, in general, will not be able to identify any of the orientations associated with these fiber populations. As an example, the simulation in Fig. 13 shows the first eigenvector overlaid on the FA map in a crossing fiber configuration (Leemans et al. 2005b). At the region where the fibers intersect, it is clear that the first eigenvector is not aligned with the underlying fiber tract configuration. With a recent study demonstrating that most WM voxels (~90 %) contain multiple fiber populations (Jeurissen et al. 2012), it should be clear that wherever possible, not DTI, but more complex models should be preferred to model fiber orientations (Tuch 2004; Wedeen et al. 2005; Tournier et al. 2007; Descoteaux et al. 2011).

WM “integrity”

“Integrity” reflects the state of being “whole”, “entire”, or “undiminished” (that is, according to the dictionary). By definition, any change in WM “integrity” as commonly indicated by the words “impaired”, “decreased”, “reduced”, “loss of”, or “abnormal” has, therefore, a pejorative sound to it. Although the term “integrity” is admittedly somewhat vague, it suggests that these DTI measures reflect the health status of WM tissue. Given the extent of several of the aforementioned confounds, such as the abovementioned “crossing fibers” issue and PV effects (Alexander et al. 2001; Tournier et al. 2011; Jeurissen et al. 2012), and the profound influence they have on DTI measures (Wheeler-Kingshott and Cercignani 2009; Vos et al. 2011, 2012) such an interpretation does not necessarily hold. However, if one is certain that only pathology is involved without any contribution from other hidden covariates that modulate the observed findings (Vos et al. 2011), using the wording “WM integrity” may be appropriate. For instance, if DTI measures change over time (e.g., alterations before and after treatment with chemotherapy) or differ between groups (e.g., patients with and without chemotherapy) while being correlated with changes or differences in cognitive

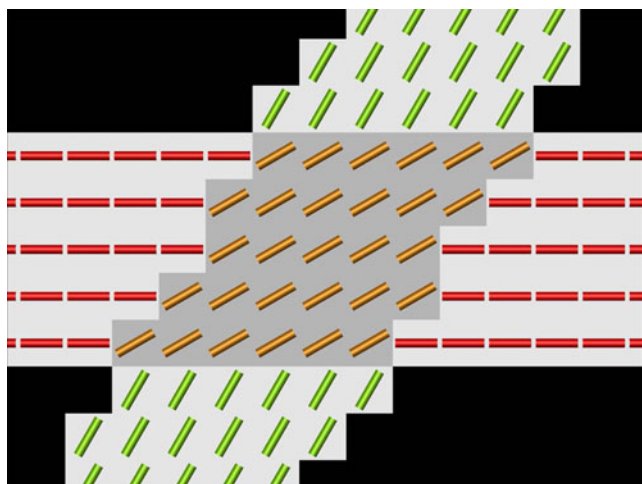


Fig. 13 Dominant diffusion orientation (first eigenvector derived from the diffusion tensor) overlaid as a cylindrical glyph on a fractional anisotropy map for a simulated “crossing fiber” configuration. In the region where both fiber tracts intersect, the first eigenvectors (shown in orange) are not aligned with the underlying fiber configuration, highlighting the inability to capture the orientations of multiple fiber populations with DTI

performance and the amount of chemotherapy exposure, it is likely that the observed DTI changes reflect a loss of “WM integrity”.

Is there still a future for DTI in a clinical context?

Undoubtedly, the answer is “Yes!”. Despite the numerous pitfalls that exist when acquiring, processing, analyzing, and interpreting DTI data (for a detailed overview see (Jones and Cercignani 2010), there is a wealth of valuable information that can be obtained, which can even be useful as priors for other functional techniques, such as fMRI (Stephan et al. 2009)) or trans-cranial magnetic stimulation (TMS) (De Geeter et al. 2012). The major difficulty when performing a DTI study is to ask the right questions given its lack in specificity. In this context, it should be clear that with DTI, it is virtually impossible to answer questions like: “Does subject “X” suffer from pathology “Y”?”. Valid questions for DTI studies, on the other hand, could include: “Where in the brain is there a difference in the microstructural organization between healthy controls and subjects with pathology “X”?”, “Is there a difference in the microstructural organization of WM fiber bundle “X” between healthy controls and subjects with pathology “Y”?”, “Can the severity of disease condition “X” be reflected by the microstructural organization of fiber bundle “Y”?”, or even “In a longitudinal (follow-up) design, what is the differential effect of medication “X” in tract “Y” for pathology “Z” on the microstructural organization?”. In each case, “microstructural organization” should be interpreted in terms of DTI based measures, such as FA, MD, RD, and AD.

It is useful to emphasize that while it may not be feasible to differentiate demyelination, axonal degeneration, or any other dynamic microstructural process, DTI may still be sensitive to these changes and could provide the basis for more detailed future investigations. For a detailed overview on how to—and, importantly, also on how *not* to—interpret findings from diffusion studies, the interested reader is referred to an excellent review by Jones et al. (Jones et al. 2012).

Guidelines and future recommendations

So far the few DTI studies that investigated chemotherapy-induced cognitive impairment used ROI-based or VBA methods and included only a limited number of subjects. As mentioned before, although DTI is a very sensitive technique in detecting WM damage, it is not specific in determining what microstructural alterations occurred; was it demyelination, axonal loss or something else? Additional new insights may come from other analysis approaches such as fiber tractography avoiding some problems that are present in VBA; “tractometry” offering more specificity in determining which therapy-induced microstructural cerebral WM changes occurred; and multi-center studies, allowing to perform longitudinal studies with more subjects and thus increasing statistical power.

Fiber tractography

Due to its fully-automated nature and the fact that no a priori hypotheses need to be made regarding the spatial location and extent of the effect of interest, VBA, such as TBSS (Smith et al. 2006), is one of the most popular tools for investigating DTI data. VBA, however, requires voxel-to-voxel correspondence across multiple data sets, which may not be guaranteed, even if advanced DTI based coregistration approaches are used (Park et al. 2003; Leemans et al. 2005a, 2006; Van Hecke et al. 2007). In addition, VBA results are known to be sensitive to the amount and type of smoothing (Jones et al. 2005; Van Hecke et al. 2010a), and template selection (Van Hecke et al. 2008b, 2009b, 2011). A promising approach to study the effect of chemotherapy on specific WM pathways that may mitigate many of these issues is FT. With FT, one can obtain more anatomically specific information than with VBA as the former can take long-distance information into account. Interpretation of FT results, however, is challenging and can be further complicated by pathology. A common misunderstanding, for instance, is that probabilistic FT approaches are considered to be more accurate than their deterministic counterparts. The former is usually based on the latter, so both suffer from the same limitations of the model that was used to

characterize the diffusion in the first place. Other unfortunate claims that have appeared in literature are (i) “*Deterministic FT methods cannot reconstruct trajectories through regions with crossing fibers.*” and (ii) “*Probabilistic DTI based FT approaches can resolve multiple fiber populations.*”. While claim (i) is only valid if the applied diffusion model (e.g., DTI) cannot deal with crossing fibers, it is incorrect if diffusion approaches are used that *can* capture the orientations from multiple fiber populations on a voxel level (Wedeen et al. 2008; Descoteaux et al. 2009). Claim (ii) is incorrect as the diffusion tensor is not able to resolve crossing fibers. Hence, any FT approach based on DTI will encounter this issue as well. Further in-depth discussions regarding FT and its interpretation can be found in recent diffusion MRI textbooks (Johansen-Berg et al. 2009; Jones 2011).

Multicenter DTI studies

As with any other data acquisition system, there are several factors that introduce variability in diffusion MRI measurements. In addition to choices of hardware configuration (field strength, coils, etc.) and options in diffusion sequence settings (b-value, voxel size, etc.), physiological contributions, such as subject motion, cardiac pulsation, and respiratory motion contribute to the variability that is inherently present in DTI data (Heiervang et al. 2006; Danielian et al. 2010; Walker et al. 2011; Heemsterk et al. 2013; Kozak et al. 2012; Kristo et al. 2012a, b). Acquiring higher-SNR data can increase the statistical power for group-based studies, but may not always be feasible given the typical time constraints in a clinical environment.

Another avenue to improve the sensitivity is combining DTI data cohorts from multiple centers (Vollmar et al. 2010; Teipel et al. 2011; Zhu et al. 2011; Walker et al. 2012). Facilitated by improvements in data access/sharing, multicenter DTI studies have gained in popularity over recent years. Despite the obvious benefits, such as increased statistical power and diversity in “subject sampling”, pooling data sets is quite complex and requires careful integration of inter-site differences that can affect the overall variability (Walker et al. 2012). Ideally, data from a physical phantom and/or one or more healthy volunteers should be acquired to estimate inter- and intra-site reproducibility and to identify potential confounds and systematic artifacts (Tournier et al. 2011). If the data are deemed “appropriate”, that is, there is no significant inter-site difference in terms of data precision/accuracy, there is no need to use correction tools for subsequent analyses. Unfortunately, this may not be the case and, hence, correction procedures will be needed that can adjust for such inter-site differences. Although suggestions on how to integrate inter-site variability have been put forward (Vollmar et al. 2010; Zhu et al. 2011), there is still no standardized way of tackling this issue. Nevertheless, it is

recommended to carefully design the acquisition protocol and investigate potential confounds that are expected to contribute to inter-site variability. Also dividing the groups (e.g., patients and healthy controls) evenly across sites is necessary to minimize the subject inclusion bias. By doing this *from the start* of a multi-center study one can avoid severe problems, which may be impossible to correct for after the data have been acquired. Further guidelines on how to initiate a multi-center DTI study and a general framework for evaluating the inter- and intra-site data variability can be found in the work of Walker et al. (Walker et al. 2012).

“Tractometry”

To really understand which aspect(s) of the WM microstructure is (are) driving the observed changes in DTI based measures, it should be clear that other complementary data and/or experiments are needed. To this end, “tractometry” has recently been proposed as a comprehensive multi-modal approach for quantifying *specific* microstructural properties along WM fiber tracts (Bells et al. 2011). Multiple MRI techniques, including quantitative magnetization transfer (qMT) imaging (Cercignani and Alexander 2006), relaxometry approaches (e.g., mcDESPOt—(Deoni et al. 2008), myelin water mapping (MacKay et al. 2006)), and advanced diffusion approaches (e.g., CHARMED—(Assaf et al. 2004; Assaf and Basser 2005) and CSD—(Tournier et al. 2007)) are combined to gain more informative WM tract measures of axon/myelin morphology, such as “axon density” and “WM myelin fraction” (Bells et al. 2011). This multimodal approach may facilitate the differentiation between different pathophysiologies related to chemobrain (demyelination or restructuration of fibers). Careful coregistration between the different quantitative maps is then needed to integrate these complementary measures along the reconstructed fiber pathways. Although ‘tractometry’, further complemented with functional imaging methods, such as fMRI, magnetoencephalography (MEG), TMS, and electroencephalography (EEG), will definitely provide a more complete understanding of brain function, clinical feasibility is still highly questionable with current acquisition times topping at least one (or two) hour(s).

Conclusion

In this review, we evaluated the use of DTI for assessing possible therapy-induced changes in the microstructure of the cerebral WM. In summary, both cross-sectional and longitudinal DTI studies in chemotherapy-treated patients have demonstrated abnormal microstructural properties in WM regions involved in cognition. These findings correlated with cognitive performance, suggesting that there is a

link between reduced “WM integrity” and chemotherapy-induced impaired cognition. Although preliminary results suggest that the observed cognitive impairment could be related to changes in the myelin structure, advanced techniques that can provide more tissue-specificity information and further basic research with animal models and postmortem brain tissues will be needed to draw firm conclusions regarding the biological mechanisms of the reported WM changes. In this context several critical considerations regarding the interpretation of DTI parameters have been presented and should be taken into account when conducting DTI analyses.

The cross-sectional nature of most of the reviewed studies highlights the need for more longitudinal studies that follow patient groups over a longer period of time. Scans and cognitive/behavioral testing will be needed at baseline, i.e., before the start of the therapy, and at repeated time intervals until several years past chemotherapy. Such data will provide important information regarding possible recovery over time or long term and/or delayed damage of the WM. In addition, longitudinal changes in DTI parameters could serve as a neuropathologic biomarker for treatment-induced neurotoxicity and will be important to follow-up on possible recovery and neurorehabilitative interventions, including behavioral and pharmacological approaches.

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