Timing stroke: a review on stroke pathophysiology and its influence over time on diffusion measures

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Abstract

Diffusion imaging (DWI) is considered an optimal technique to detect hyperacute cerebral ischemia and has thus enriched the clinical management of patients with suspected stroke. Researchers have taken this technique beyond with Diffusion Tensor Imaging (DTI)-extracted measures, which have been proposed as biomarkers of stroke progression. A large body of literature report on the correlates between pathophysiological events, such as cytotoxic and vasogenic edema, and diffusion changes in the brain. However, a unified picture of these changes, and their exploration as stroke pathology progression biomarkers, remains to be done. We present here a narrative review on the different pathophysiological events underlying stroke from onset until late subacute stages and its relation to different brain edema forms. Studies included in this review used either DWI and /or DTI analysis in hyperacute (<24h), acute (1-7 days), early subacute (7-30 days) and/or late subacute (1-6 months) phase of stroke, including human and animal models. Our conclusions are that diffusion measures should be considered as a potential proxy measure for stroke neuroinflammation status, specially in early stages of the disease. Furthermore, we suggest that the choice of diffusion measures and the interpretation of their changes, in both research and clinical settings, need to be linked to the different stroke phases to account correctly for the progression, and eventual resolution, of neuroinflammation.

Keywords : diffusion imaging, DTI, white matter, stroke, cytotoxic edema, vasogenic edema

1. Introduction and purpose of the review

Visual assessment of diffusion-weighted imaging (DWI) has increasingly become one of the most reliable sequences to diagnose stroke in acute clinical settings [1], specially in cases where conventional MRI or CT do not offer the same sensibility. Benefits from DWI include acquisition of clearer anatomic details in acute lesions [2] and more sensitivity to tissue alterations [3]. Moreover, DWI modeling through diffusion tensor imaging (DTI) has been considered as a promising techniques in neuroradiology of the last decades [4], adding quantitative information in the study of stroke [3]. However, quantitative analysis with DTI depends on two important factors. First, the outcome itself depends largely on the type of pipeline implemented to analyse the images and extract quantitative measures. In short, the choice of a good post-processing method remains important [4]. Second, the interpretation of these results depends on both the knowledge on biological processes that occur at the time of image acquisition, as well as baseline subject's characteristics (pathological status of the patient, moment of acquisition during the pathology course, etc.). In other words, stroke-related mechanisms, such as protein and water accumulation, influence measures extracted through DTI [5], and a good distinction between those pathological processes and their impact on DTI-derived measures may improve early diagnosis and prognostic from the early stages.

We present here a narrative review of the temporal changes of DTI measures through the post-stroke inflammatory process, from the hyperacute phase up to the early chronic stages of the disease. The sources for this review are from both clinical and basic research scientific studies retrieved from the MEDLINE® database, using terms such as "stroke" AND/OR "diffusion imaging/DTI/DWI" AND "edema". Studies that were selected had to be conducted during the timing frame of post-stroke neuroinflammation: acute phase (from onset to 1-week post-stroke), early subacute phase (from 1-week to 1-month), late subacute (from 1 to 6 months). Due to variation in the formal definition of these phases, no keywords for the phases were chosen; instead, after a thorough review of the articles it was decided if the timing used in the studies was appropriate for our scope. To complement the information retrieved from these articles, we will summarize in a descriptive and compiling fashion the main events of stroke pathophysiology that influence water diffusion in brain, and in the end will discuss which factors are more related to diffusion changes. We preferred a narrative review to help both researchers and clinicians engage from the same baseline of knowledge of diffusion imaging and neuroinflammation. In our experience, experts in one of these fields are not necessarily familiar with details from the other, and we want to offer a detailed vision of both fields to frame our question better. We also aim to discuss the role of the different forms of brain edema as the bridge between diffusion changes and the pathophysiology of the different phases in stroke progression.

2. Brief overview on DTI measures

Application of diffusion gradients during DWI data acquisition allows for a comparison of water restriction levels between tissues in a more subtle way than standard MRI sequences do [6,7]. The interest in DWI grew rapidly when methods for quantifying this water movement per voxel of the image were developed. The most used method to date is DTI, in which the diffusivity in each voxel is modeled through vectors, each one representing a possible direction of water diffusion in the voxel, as well as its magnitude (quantity of diffused water). These vectors are summable into one unique vector that summarizes the characteristics of the diffusion [1]. As any model, this is an approximation to the reality, broadly used since the connection betwen these ellipsoids can draw easily the different white matter structures (WM) of the brain when images are co-registered with brain atlases [8]. As a result, changes in water diffusivity can be measured either at global level or per regions of interest, allowing us to compare diffusion in the different brain regions and tissues. For instance, the identification of hindrance to movement helps delineating different structures, but also helps identifying pathological signs such as necrosis core in stroke [9].

WM offers more restriction to water diffusion than grey matter, because of the delineation that the axonal walls impose on the water, limiting the number of directions for diffusion [7]. Diffusion can be expressed as the quantification of water movement in each possible direction of the ellipsoid, commonly called **diffusivity**. The two basic diffusivity measures are: 1) **axial diffusivity** (**AD**, also called longitudinal diffusivity, $\lambda\parallel$ or λ_1), which represents the diffusivity along the major vector of the ellipsoid, i.e. parallel to the major direction of a white matter tract; and 2) **radial diffusivity** (**RD**, also called perpendicular diffusivity, $\lambda\perp$ or), which represents the average of the directions that go perpendicular to the major vector, i.e. the vectors that represent the width-breadth of the diameter of a tract. With these two measures, three vectors for any ellipsoid can be defined. The combination of the three vectors is called **Trace (T)**, or overall water content ($T = \lambda_1 + \lambda_2 + \lambda_3$) and represents the overall diffusivity in one voxel. It is common in clinical and research settings to calculate maps with the averaged information of T. The more well-known measure of **Mean Diffusivity** (**MD**, or Apparent Diffusion Coefficient, **ADC**) can easily be generated with these data, which is estimated as . Beside diffusivity, diffusion can also be expressed through directionality of water, also called degree of anisotropy. Tensor models (i.e. DTI) imply that the **directionality** can be represented as a continuous degree from **isotropy** (equal directionality of water in all directions from a reference point) to **anisotropy** (unequal diffusion, where one direction is usually predominant over the others) [10]. The most widely used anisotropy measure is **fractional anisotropy (FA)**, which is defined as $FA =$, or the degree of anisotropy on account of the three vectors (to note, whereas diffusivity measures have mm^2/s as unit, FA is an adimensional measure). It is common practice to elaborate brain maps of FA and/or MD, where each voxel of a selected region (or overall brain) is labeled with the measure of interest. By doing so, a comparison of the same area between different individuals or against standard values is possible.

[Insert figure 1 here]

Figure 1. Simplified representation of ellipsoid modeling on water diffusion in nervous tissue. Diffusion measures represent both the level of isotropy, of free movement of water in a space (represented in the middle part of the picture) and the amount of diffusion per each of the directions of the ellipsoid (represented by the size of the ellipsoids and the eigenvectors $\lambda\perp$ and $\lambda\parallel$). When water diffuses freely, the FA is closer to 0, since the shape of the ellipsoid is more similar to A (in the panel), and closer to 1 when the shape of the ellipsoid is more similar to B, and it will be more similar to the original value in a different space with more diffusion (A′). Since water diffuses mainly in the extracellular space, diffusivity (RD, AD and MD) will be more represented by diffusion in this compartment than from intracellular spaces (which offer more restriction to movement). Therefore, spaces with more free diffusion (such as brain ventricules) will show lower FA, but higher diffusivity values, whereas white matter tend to show higher FA and lower diffusivity values.

2.2 Limitations on diffusion measures interpretation

Although the literature shows that part of the popularity of DTI measures is due to the interpretations between measures and microstructure integrity, specially in relation to lesioned fiber bundles [3,4,11–13], caution should be taken for different reasons. First, different factors may alter water diffusion in ways not directly related to the pathological ongoing process. These situations should be addressed when extracting, analyzing, and interpreting data. For example, recent studies have shown that normal aging has an effect on WM fiber bundles that is comparable to those observed in studies on Alzheimer's disease (e.g., Montal et al., 2017), or similar to certain conditions, such as obstructive sleep apnea [15], where there is an ongoing neuroinflammation process. Free water modeling, which indicates the proportion of unconstrained water in a voxel, can be considered as a complement to decide how much diffusion measures account for pathophysiological processes or whether they simply reflect the presence of water [16].

Secondly, tensor modeling presents certain limitations in relation to fiber tract reconstructions, which could limit interindividual comparisons. These include voxels containing multiple crossing fibers [17], uncorrected presence of cerebrospinal fluid [18] or the partial volume effect [19]. Considering the methodological limitations of tensor-based analysis and the fact that tractography is not widely used in clinical settings, this review will concentrate on the impact on studies reporting measures extracted from voxel-shaped brain diffusion maps.

3. Pathophysiology of ischemic stroke neuroinflammation

In the process of ischemia, which accounts for up to 87% of stroke cases in the last decades [20], the interruption of blood supply to the brain involves a lack of glucolytic substrate and oxygen supply. This metabolic imbalance triggers an immediate inflammatory response damaging all cellular populations in the nervous tissue, whose duration will depend on factors such as the timing of reperfusion. However, ischemic strokes elicit both intracellular and extracellular pathologic processes that will demarcate the necrotic core, the surrounding areas (i.e. penumbra) and the variation in the restriction of water in both compartments. In this section, we will summarize the course of events in the progression of stroke and the main pathological entities that are crucial to our review, i.e., cytotoxic and vasogenic edema.

3.1. Stroke-related brain edema: cytotoxic edema

Ischemia triggers the depletion of energetic resources, due to sudden lack of oxygen and glucose intake. If ischemia reaches a severe level, a series of molecular cascades will lead to an unbalanced ion and water influx into the cells, producing **cytotoxic edema**. This inflow, along with a failure of membrane transporters due to the lack of ATP, leads to an expansion of the cytoplasm with an eventual break down of the membranes. Cytotoxic edema occurs within minutes after stroke onset, but there is a large variability in the appearance of clinical and radiological signs among individuals [21]. It is estimated that its peak is reached

at 24h, after which there is a decline due the cleansing performed by immune cells such as Neutral Killers (NK), activated astrocytes and the disintegration of cellular bodies [22].

In the natural course of ischemia, the first and most damaged cells will form the **necrotic core**, and the surrounding surviving cells will form the **penumbra tissue**. Necrosis can expand to the surrounding areas due to a further degradation and eventual destruction of other membranes, enhanced by excessive releases of glutamate, which exacerbates the influx of Ca^{2+}; or via Ca^{2+}-activated enzyme-driven degradation. This is not only linked to damaged neurons but also surrounding glial cells [23]. Released intracellular molecules (such as damage-associated and pathogen-associated molecular patterns, DAMPs and PAMPs respectively) will consequently work as inflammatory signals. Another source of signaling molecules comes from destruction of oligodendrocytes (OD), with a degradation of myelin sheaths and axons, which has been reported since the appearance of ischemia [24]. Myelin is degraded through a first swelling step (**intramyelin edema**) and a posterior, more active retraction and degeneration [25]. Axon degeneration is characterized by a beading process, where axon nodules adopt bead shapes [26], with each bead containing a portion of the accumulated water and debris. This new configuration will have effects on the traceable water diffusion, as we will discuss later.

3.2. Stroke-related brain edema: vasogenic edema

The second process raised after unspecific inflammation is **vasogenic edema,** also called extracellular edema [22]. This is part of the extended cell-dominant inflammation which reaches its peak around 3-5 days after an ischemic stroke onset [27]. It is estimated to last from several days to 1 week (or even weeks), but the timing of its resolution has not been well documented to date [28]. Vasogenic edema is characterized by both a rise of fluid and cellularity (space occupation by cell bodies, both in number and body density) in the perineural space. The process develops as follows: after the release of signaling molecules from damaged microglia and neurons, activated glia (including astrocytes) emit cytokines that break down the different unions of the brain blood barrier, and thus it creates an influx of water (along with an inbalance of Na^+) from the blood stream into the perineural space. This causes a mass effect on the neural bodies, also known as ionic edema [28,29]. Cellularity rises during the first 24 h due to both hypertrophy of reactive glia and leukocyte migration through the disrupted blood barrier [30]. Moreover, infiltrating leukocytes release enzymes to degrade the conjunctive unions (astrocytic end-feet) as well as the interstitial matrix itself to create space to foster further upcoming cells [31]. This barrier disruption overlaps in time with the imbalanced Na^+ influx due to membrane transport disruption, and therefore it is argued that vasogenic edema is also an extended part of ionic edema [32].

In its final stage around 7-10 days after onset [33], activated astrocytes generate longer neurites which will form the glial scar, favoring the healing of damaged tissues in the brain, albeit preventing the immediate migration of neural stem cells to the necrotic cores [34]. Parallely, axonal total breakdown can be seen when either T-cells elicit specific cytokines (IL-1, IL-6, IFN-γ) at the peak of inflammation, or when large injuries

are present in the axons, leading to a slow process of axonal and (eventual) Wallerian degeneration. This inflammatory component has also been found very similar to that found in Multiple Sclerosis [35].

In summary, there is a clear difference between a hyperacute and unspecific inflammatory response (from hours to 48 h after onset) that involves cytotoxic edema and neuroexcitatory shift, and a consequent more specific immune response (from 2-5 days after onset) that leads to vasogenic edema and cytokine storm.

3.2. The chronic aspect of neuroinflammation

Regardless of the type of edema, the chronicity of neuroinflammation is a relevant question in the follow-up of stroke survivors. Longitudinal studies can benefit from taking into account all factors that may alter inflammation for better defining changes during the course of stroke. Functional recovery has often been linked to changes in underlying structures during physiological recovery, such as enhanced sprouting, better synaptic regulation or migration of vascular and neural stem cells [36–38]. However remaining inflammatory mediators can create an imbalance that prevents proper recovery from happening. Necrotic lesions gradually acquire an inflammatory profile in the long-term due to immature vessel repair and inefficient glial scars, augmenting the presence of inflammatory mediators (e.g., astrocyte-mediated vascular endothelial growth factor [VEGF], neurotrophic factors, TNF-α, IL-12, etc.) [39–42]. Some authors have suggested that chronic inflammation is due to other causes overlapping in time with the decrease of the earlier inflammation processes, such as autoimmunity directed to new myelin formation [27] or the recirculation of cytokines from spinal fluid [43]. Even if the presence of those mollecules has arguably fewer deleterious effects than when they were released in earlier phases of the disease, the scope of their effects in later phases remains to be explored. Therefore, it is not impossible that destruction of axons along with deficient 8ascularr structure renewal leads to a persistent edema in nervous tissue, and most importantly, this could presumably have an influence on diffusion dynamics and their expected changes in the course of recovery.

4. Dynamics of diffusion tensor measures in the course of stroke

In this section, we are going to summarize the dynamics of DTI measures for the different time points that have been mostly used in stroke recovery in literature. The definition of the different phases can be somewhat problematic since the timings observed for each phase are not homogenous among the various studies, but a scientific consensus exists for the main timepoints of post-stroke recovery [44]. Three phases with an approximated estimation for each one will be presented, to set a chronological order of possible changes in DTI measures: acute phase (from onset to 3-5 days), early subacute phase (from 1 week – 3 months) and late subacute phase (from 3 months on).

4.1.1. Acute phase of stroke and cytotoxic edema

Cytotoxic edema is the first histopathological phenomenon observed after an ischemic injury. Diffusivity is mostly captured in extracellular space, and since cytotoxic edema causes an intracellular water and ion accumulation, this phase has been linked to an immediate decrease of AD [3,12,28], and with an appearance of more hyperintensities in the first hours. RD, on the contrary, shows an increase due to myelin edema [12,25,45,46].

Studies with animal models have found a decrease in MD, and even in FA, in the hyperacute phase of stroke [25,47]. Although a decreased level of FA has been reported in different cases of hypoperfused tissue [48], changes in MD, along with AD and RD, seem to be much more stable and predictable than those in FA [49–51]. FA changes are directed by structural changes in the extracellular space, and therefore even if diffusivity (i.e., quantification of water movement) is low, we can encounter a maintenance (or even increase) in the directionality of these fluids, which does not reflect the underlying damage to neuronal structures [50,52]. However, in several longitudinal studies, FA seems to show a continuous decrease as a result of the eventual axonal degeneration [53–55], but since conflicting evidence have been reported, it is unsure to rely on the FA dynamics to define intracellular edema, unlike the more predictable changes in diffusivity measures, such as MD.

4.1.2. Dynamics of DTI measures during acute phase

During this early phase, three precise moments of the stroke course have been investigated more attentively:

- **Up to 6-7 hours** after onset the commonest findings are a decrease of AD, MD and FA, with a possible increase of RD in general brain maps [12]. Since in this early phase only cytotoxic edema is expected to damage neural tissue, regaining a good perfusion to rise oxygen and glucose levels is a priority [56]. It remains challenging to distinguish persisting necrotic tissue from the one with recovery potential based on these markers, on one hand due to lack of follow-ups in most studies with human participants, and on the other hand due to the difficulty of defining quantitative thresholds for this distinction. However, some studies have shown that hypoperfused tissue with recovery potential shows slightly higher FA values than lesioned tissue with worse prognostic [18,48]. Others have shown that diffusivity measures may have a potential value as early predictors. For instance, Alegiani and colleagues [18] found that tissue that was labeled as necrotic at baseline (mean time 1 = 3h), but that had been labeled as “recovered” after 2 days, recorded increases of MD along with AD and RD at early stages (mean time 2 = 6h), whereas FA was always decreasing, albeit at a non-significant rate. Others, however, have not found a relation between early edema resolution and reperfusion via thrombolysis [57]. With these pieces of evidence, as a way to predict viability of the tissue, and even to predict smaller size of swelling [58], MD seems more sensitive and solid as a measure without comparison to a second MRI scan [48,50].

- **Around 24 h hours** after onset, the highest peak of the unspecific inflammatory response is taking place. Accordingly, the appearance of intramyelin edema at this point has been associated with further decrease of AD and an increase of RD. Further decreases of MD and FA are expected, as it has been shown in animal [24] and computational models [59], although other studies have shown no changes in anisotropy [60]. **Between 24 and 48 hours** post-onset, axon and myelin degradation are expected, which should be reflected by a decrease in (return-to-normal) RD, linked to the disappearance of the bead conformation [61]. Although areas with slight increases of FA have been related to less presence of hyperintensities [18], this increase may also be related to the nature of calculation of FA, in the case that RD values have not normalized after intramyelin edema [52]. More commonly seen, decreases of FA, MD or other diffusion measures in severe non-reversible damaged areas have been interpreted as a consequence of increasing cellularity [18,59,60], which announces a more severe injury than expected. In other words, low diffusivity values seem to predict better the (non) resolution of hyperintensities and lesion progression than anisotropy estimation alone at this timing [62]. This hypothesis should be taken with caution, since differentiation between reversible and irreversible tissues with just diffusion values has not been accurately done to date until inflammation peak is over, much later in stroke course [55].

- **Between 3 and 7 days**, the effects of ionic and vasogenic edema begin to overpass cytotoxic edema, increasing MD into stable levels [3], seemingly also increasing AD and RD at a steadfast pace [18]. One study found that the rise in MD during this period (onset – 5 days) was a good predictor of long term outcomes, although the patients included in the study had suffered from hemorrhagic strokes, and therefore perfusion changes may have shown more impact than in ischemic pathology [63]. One study has even found that a lower reduction of FA at this stage (compared to baseline) is associated with a better outcome at 3 months. [55]. This could suggest that changes of FA are more sensitive to vasogenic edema presence and that FA could therefore be considered a reliable measure to interpret underlying pathological status at this time point. Although some authors have suggested that edema-corrected lesion volume in diffusion MRI could be already estimated at this time point [64], the timing for vasogenic edema resolution is still a matter of discussion [65].

4.2.1. Subacute phase of stroke and vasogenic edema

In the case of vasogenic edema, a rise in diffusion in the extracellular space (i.e., more water restriction inside neural structures) is going to cause effects opposite to those of cytotoxic edema. A rise in diffusivity measures (specially MD and AD), along with axon beading (which causes a rise in RD if myelin has not disintegrated), may lead to what has been called pseudonormalization of diffusivity [26]. This has been reported from 2-3 days to one week after stroke onset [66,67], coinciding with the triggering of mechanisms for specific immunity-related inflammation in the brain, at least 3-4 days after the onset. Pseudonormalization is defined as a false “return” to normal values: after a breakdown of the barriers

diffusion of water is increased in the perineural space, which rises the levels of diffusivity. Thus, caution must be taken when interpreting these dynamics as a sign of microstructural stability. Here, FA seems to have a stronger negative correlation with the persistence of edema.

Axonal failure and the combination of other damaging factors (e.g. cytotoxicity elicited by released mediators) might cause a faster negative pattern in FA. A prompt decrease in FA has proved to be a good predictor of lower outcomes in later stages [68], and studies using animal models have helped distinguishing this specificity, since the decrease in FA is better profiled at the beginning of the subacute phase of inflammation, and showing a higher correlation to extracellular water accumulation [59,69]. These pieces of evidence suggest that FA is a more stable and sensitive measure to reflect the actual state of the white matter tracts in presence of extracellular edema in later stages, even to define the reversibility of lesioned areas, than other diffusion measures [69,70].

4.2.2. Diffusion dynamics in early subacute stroke phase

This phase is roughly defined as the end of the acute phase (around 5-7 days after onset) and the first weeks after stroke onset. It is acknowledged that edema (understood at least from vasogenic origin) will be observed until at least one month post onset [65]. A suggested utility for this timepoint is to evaluate the reversibility of lesioned tissues after the inflammation peak. The challenge of this goal, as pointed by Nagaraja and colleagues, is to separate the pseudonormalization of diffusivity from the real resolution of lesions [71]. As these authors point out, even if the clearance of hyperintensities and stable diffusion measures are related to reversibility of lesions, the pseudonormalization may hide underlying pathological conditions [71].

In one week to two weeks after onset, we expect to see an either steadfast elimination of edema signs, or the stabilization of those radiological signs. However, seminal studies showing stabilization of measures after 7 days encounter contradictory data regarding the reliability of these measures. Either from perfusion measures in humans [72,73] or histological examination in animals [25,74], real presence of lesioned tissue presented a mismatch with diffusion maps. This suggests that normalization of diffusivity measures does not necessarily reflect a resolution of infarcted areas (as seen with MD in earlier timepoints), and in milder cases pseudonormalization would prevent the analysis of the reversibility potential. It is possible that lower baseline diffusivity is associated to a permanent presence of hyperintensities, in other words, an early indicator of low probabilities of reversibility [73]. Interestingly, a decrease in diffusivity values in the subacute phase has been linked to a rise of FA in lesions with infarct expansion going on, suggesting that intracellular edema can still not be resolved at this stage [18]. Anisotropy could represent a reliable measure to distinguish the presence of edema in later phases. Moreover, stability of anisotropy between acute and early subacute time points would reflect fewer damaging effects from vasogenic edema, and therefore probably more integrity of vascular structures after neuroinflammation.

[Insert table 1 here]

Table 1. Direction of the changes in the different diffusion measures and in the number of Hyperintensities (HI) in different articles (measures were chosen as they were the most reported ones across studies). Blue symbols indicate studies with humans, green symbols indicate studies with animals. Symbols refer to the value in the specific timepoint in comparison to a reference value, being this value either immediately priorly known value, or a value in the contralateral homologue area. Only studies with values that were reported as significantly different from the reference values are included in the table.

Phase \ DTI measure	**AD**	**RD**	**MD**	**FA**	**HI**
Hyperacute (0-6 h)	↓ (Pitkonen et al., 2012) ↓ (Sun et al., 2006) ↓ (Alegiani et al., 2019)	↓ (Pitkonen et al., 2012)[1] ↑ (Song et al., 2002) ↓ (Alegiani et al., 2019)	↓ (Pitkonen et al., 2012) ↓ (Nael et al., 2015) ↓ (Harris et al., 2004) ↓ (Alegiani et al., 2019)	↑/↓ (Bhagat et al., 2008)[2] ↑/↓ (Liu et al., 2007)[2] ↑/↓ (Nael et al., 2015)[3] =/↓ (Pitkonen et al., 2012) = (Harris et al., 2004) = (Alegiani et al., 2019)	↓ (Ringer et al., 2001)
Early acute (up to 24 h)	↓ (Pitkonen et al., 2012)	=/↑ (Pitkonen et al., 2012) =/↑ (Shereen et al., 2011) ↑ (Alegiani et al., 2019)	=/↑(Song et al., 2003) ↓ (van Gelderen et al., 1994) ↓ (Zhang et al., 2018) ↓/↑ (Alegiani et al., 2019)	↓ (Pitkonen et al., 2012) ↓ (Song et al., 2003) =/↓(Alegiani et al., 2019) = (van Gelderen et al., 1994)	↓ (Albach et al., 2013)
Late acute (3-5 days)	= (Alegiani et al., 2019)	= (Alegiani et al., 2019)	↑ (Kidwell et al., 2000) ↑ (Axer et al., 2007) ↑ (Song et al., 2003) ↑ (Ringer et al., 2001) =/↓ (Alegiani et	↓(Axer et al., 2007) ↑/↓(Alegiani et al., 2019) ↓(Song et al., 2003)	↓ (Albach et al., 2013)

			al., 2019)		
EARLY Subacute (1 week -1 month)	=/↑ (Song et al., 2003)	↑ (Song et al., 2003)	↑ (Srivastava et al., 2008)	↓ (Song et al., 2003)	
LATE SUBACUTE (> 1 month)	↓ (Visser et al., 2019) ↑ (Alegiani et al., 2019)	=/↓(Visser et al., 2019) ↑ (Alegiani et al., 2019)	↓ (Visser et al., 2019) ↑ (Alegiani et al., 2019)	↑ (Wardlaw et al., 2017) =/↑(Visser et al., 2019) ↓ (Alegiani et al., 2019) ↓ (Pinter et al., 2020)	↓ (Battey et al., 2014)

[1-] Analysis was done at 2-3 h post-onset, considered extremely early to see changes in myelinated structures [12].

[2-] Both studies with this note had exactly n=3 participants whose results showed a rise in this measure. The rest of participants showed the opposite tendency.

[3-] This study showed a dissociation between necrotic tissue (decrease in FA) and hypoperfused tissue (rise in FA).

4.3. Late subacute phase of stroke and beyond

Late subacute phase of stroke is commonly referred as the time between 3-6 months after onset, although some authors may count from 1 month after onset until the beginning of the chronic stage. It is widely accepted that spontaneous biological changes after this timepoint are limited [73], and thus further changes must be linked to more active therapies. Studies often report functional changes in stroke patients at long-term follow-ups and after treatment and/or rehabilitation, linked to structural changes [75] or resolution of lesion markers such as hyperintensities [76]. However, changes in this phase seem to follow a more complicated pattern than in earlier phases of the inflammation. This is probably due to pre-stroke conditions, quality of health management after stroke and status of neuroinflammation.

One of the hypotheses to explain the conflicting results is the presence of some level of vasogenic edema, which can maintain the tendency of DTI measure changes started in previous phases [77]. In other words, prevalent vasogenic edema can procure steadfast decreases of FA and stabilization and normalization of diffusivity measures. A recent study has showed this decreasing tendency in FA in the longer term, controlling for extent and location of lesion [55]. If, for example, FA values are more affected than those of MD, with AD and RD values still out of standard ranges, it could be interpreted that a defective re-

myelination is occurring, which is a sign of chronic inflammation [55]. Some authors have pointed out that these effects are due to a chronic inflammation targeting the repaired structures [27,29], maintaining a vasogenic edema effect, that can either increase FA (interpreted as recovery) or maintain its decrease (interpreted as a defective recovery). The relation between functional outcomes and this decrease in FA has also been reported [12,18,55].

However, the same diffusion changes defined as "recovery signs" have not always been found at this timing. For example, Visser and colleagues reported no changes in ipsilesional diffusion measures comparing baseline to 3 months, but they found changes in the contralesional homologue ROI [78], which was interpreted as a sign of perfusion recovery. Some authors have argued that a smaller lesion extent tends to provoke more changes in diffusion [66,79]. Interestingly, a large cohort study reported that patients with larger lesions showed the same amount of baseline FA than patients with the smallest lesions, but the former ones showed fewer white matter hyperintensities at one year follow-up, this reduction being also related to better blood pressure and less recurrency of cardiovascular events [76].

In sum, multiple causes, mainly pre-stroke conditions as well as management of vascular risk factors after stroke, influence diffusion at stages near to chronicity. However, it seems difficult to assert a link between diffusion changes and inflammation outcomes in this phase. Therefore the use of diffusion as a biomarker of chronic neuroinflammation remains to be confirmed. Nonetheless, diffusivity changes (e.g., normalization of AD, RD, MD) seem to be related to recovery and better functional outcomes, leaving the meaning of FA changes as the question to be explored.

[Insert Figure 2]

Figure 2. Interpretation of temporal changes in diffusion measures parallel to inflammatory cascades in the timeline of stroke development. The curves have been fashioned after observation of diffusion changes and parallel information, such as histopathology, perfusion measures or functional outcomes, observed in the reviewed studies (see table 1). Panel A represents the scenario where structures are less damaged and there is less remaining inflammation after the first month. Panel B represents the scenario where structures are more damaged and there is the possibility of remaining chronic inflammation.

5. Current limitations and future avenues

We must address the issue that all studies that have been mentioned in this review use voxel-based brain analysis, expressed in general maps of diffusion measures, instead of analyses of specific white matter tracts. This choice has clear reasons. First, although DTI technique is being used in clinical settings to produce brain diffusion maps, limitations of DTI analysis stands in the analysis of voxels in which crossing fibers are encountered, specially in larger lesions. Using the model of only one ellipsoid, it is not clear which white matter fiber the tensor is modeling in the given voxel [17]. Correction for other fluids such as cerebrospinal fluid [18] or the partial volume effect [19] have also been identified as limitations of this technique. However, a growing corpus of research shows that the use of fiber tract reconstruction, despite the above mentioned problems, has proven in the last decade a strong relation between topological characteristics of lesions, lesion size and functional outcomes, regardless of acute therapy or rehabilitation involved [80–82] Non-tensor modelizations of diffusion, such as HARDI (high angular resolution diffusion imaging) use probability density functions, in other words, building up a function of multiple possible directions for every single voxel, which account for a better processing of difficult anatomical points [83]. Finally, fiber tracking posits several problems to the final implementation in clinical settings. Currently, due to longer acquisition times and more complex coding, non-tensor techniques have not reached a good trade-off for clinical settings, although this had already been suggested for a decade now [77]A disconnection between software developers, diffusion users' community, researchers and clinicians slows down the overcome of these pitfalls. Improvement of time acquisition and analysis time, as well as implementation of this technique in stroke units, is undeniably part of the solution. The creation of new tractography pipelines can start the shift form DTI analyses to models that include more directions and than enable more realistic modelizations of the tracts [84], which have shown good reproducibility in recent studies [85].

DTI measures can be understood as the signature of water in its movement through and around brain structures. The simplicity of the technique itself is, however, overshadowed by the possibilities of processing and interpretation of the data. Studies based on DTI parameters on stroke should check on several points to ensure an optimal interpretation: 1) Are the changes (compared to a control sample) typical from the timepoint after stroke onset?; 2) Are these changes accountable by biological factors such as lesion size, perfusion rates or specific medical conditions?; 3) What is the best way to analyze the parameters in the sample of interest (i.e., whole brain maps, maps per region, lesion load analysis or fiber reconstruction)? Some of these questions have been addressed in already published work, such as functional diffusion maps, extensively used in brain tumor diagnostic [86]Moreover, new ways of analyzing water restriction may be developed, or may be retaken in new approaches, or in combination with other techniques. Promising ideas such as Myelin Water Fraction [87] or mediator analysis of these changes in a more data-driven way [88]are promising ideas to find the true correlates of pathophysiology of stroke in diffusion imaging.

The clinical interest on using diffusion to assess neuroinflammation status is obvious, since it is difficult to have a direct picture of the biomolecular status of the brain right after stroke. Diffusion imaging remains as a gold standard recommendation for stroke diagnostic in case of doubt upon symptomatic presentation [89]. Here DTI becomes a good candidate to test the relation between diffusion changes (e.g., signs of edema) and inflammatory markers (e.g., interleukins). If a correlate exists, then diffusion measures could be proposed as a proxy for persistent inflammation in the long-term. Researchers and clinicians interested in stroke could use this technique for a better management and monitoring of risk factors at patients follow up, as well as for studies aiming to investigate the efficiency of new therapies.

Conclusion

To sum up, diffusion imaging has proven to be a good tool for the prompt and sensitive identification of ischemic stroke, but its potential as a follow-up tool seems to be underused in stroke units. DTI, albeit its caveats, is a technique that can be honed and implemented so that clinical data will be better studied in a nearby future. We expect with this review to encourage clinicians and both neurobiology and neuroimaging researchers to combine both fields in order to obtain better descriptions of what underlies the course of stroke form the hyperacute phase.

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References

1. Soares JM, Marques P, Alves V, Sousa N. A hitchhiker's guide to diffusion tensor imaging. Frontiers in Neuroscience. 2013; DOI: 10.3389/fnins.2013.00031
2. Lin M, Liebeskind DS. Imaging of Ischemic Stroke. CONTINUUM Lifelong Learning in Neurology. 2016;22(5):1399–423. DOI: 10.1212/CON.0000000000000376
3. Curran KM, Emsell L, Leemans A. Quantitative DTI Measures. In: Diffusion Tensor Imaging: A Practical Handbook. 2016. p. 65–87. DOI: 10.1007/978-1-4939-3118-7
4. Tae W suk, Ham BJ, Pyun SB, Kang SH, Kim BJ. Current Clinical Applications of Diffusion-Tensor Imaging in Neurological Disorders. Journal of Clinical Neurology. 2018;14(2):129–40. DOI: Doi.org/10.3988/jcn.2018.14.2.129
5. Duering M, Finsterwalder S, Baykara E, Tuladhar AM, Gesierich B, Konieczny MJ, et al. Free water determines diffusion alterations and clinical status in cerebral small vessel disease. Alzheimer's and Dementia. 2018;14(6):764–74. DOI: 10.1016/j.jalz.2017.12.007

6. De Figuereido EHMSG, Borgonovi AFNG, Doring TM. Basic Concepts of MR Imaging , Diffusion MR Imaging , and Diffusion Tensor Imaging. Magnetic Resonance Imaging Clinics of NA. 2011;19(1):1–22. DOI: 10.1016/j.mric.2010.10.005

7. Rowe M, Siow B, Alexander DC, Ferizi U, Richardson S. Concepts of Diffusion in MRI. In: Diffusion Tensor Imaging: A Practical Handbook. 2016. p. 23–35. DOI: 10.1007/978-1-4939-3118-7

8. Froeling M, Pullens P, Leemans A. DTI Analysis Methods : Region of interest analysis. In: Diffusion Tensor Imaging: A Practical Handbook. 2016. p. 175–82. DOI: 10.1007/978-1-4939-3118-7

9. Sotak CH. The role of diffusion tensor imaging in the evaluation of ischemic brain injury - a review. NMR in Biomedicine. 2002;15:561–9. DOI: 10.1002/nbm.786

10. Le Bihan D. Apparent diffusion coefficient and beyond : What diffusion mr imaging can tell us about tissue structure. Radiology. 2013;268(2):318–22. DOI: 10.1148/radiol.13130420

11. Moulton E, Magno S, Valabregue R, Amor-sahli M, Pires C, Lehéricy S, et al. Acute Diffusivity Biomarkers for Prediction of Motor and Language Outcome in Mild-to-Severe Stroke Patients. Stroke. 2019;50:1–7. DOI: 10.1161/STROKEAHA.119.024946

12. Winklewski PJ, Sabisz A, Naumczyk P, Jodzio K, Szurowska E, Szarmach A. Understanding the physiopathology behind axial and radial diffusivity changes-what do we Know? Frontiers in Neurology. 2018;9(FEB). DOI: 10.3389/fneur.2018.00092

13. Ivanova M V, Yu D, Dragoy O V, Shklovsky VM, Dronkers NF. Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia. Cortex. 2016;85:165–81. DOI: 10.1016/j.cortex.2016.04.019

14. Montal V, Vilaplana E, Alcolea D, Pegueroles J, Pasternak O, Gonz S, et al. Cortical microstructural changes along the Alzheimer's disease continuum. Alzheimer's & Dementia. 2017;14(3):340–51. DOI: 10.1016/j.jalz.2017.09.013

15. Baril AA, Gagnon K, Descoteaux M, Bedetti C, Chami S, Sanchez E, et al. Cerebral white matter diffusion properties and free-water with obstructive sleep apnea severity in older adults. Human Brain Mapping. 2020;41(10):2686–701. DOI: 10.1002/hbm.24971

16. Dumont M, Roy M, Jodoin PM, Morency FC, Houde JC, Xie Z, et al. Free Water in White Matter Differentiates MCI and AD From Control Subjects. Frontiers in Aging Neuroscience. 2019;11(October):1–9. DOI: 10.3389/fnagi.2019.00270

17. Farquharson S, Tournier JD. High Angular Resolution Diffusion Imaging. In: Diffusion Tensor Imaging: A Practical Handbook. 2016. p. 383–406. DOI: 10.1007/978-1-4939-3118-7

18. Alegiani AC, MacLean S, Braass H, Gellißen S, Cho TH, Derex L, et al. Dynamics of water diffusion changes in different tissue compartments from acute to chronic stroke—a serial diffusion tensor imaging study. Frontiers in Neurology. 2019;10(FEB):1–7. DOI: 10.3389/fneur.2019.00158

19. Szczepankiewicz F, Lätt J, Wirestam R, Leemans A, Sundgren P, Westen D van, et al. NeuroImage Variability in diffusion kurtosis imaging : Impact on study design, statistical power and interpretation. Neuroimage [Internet]. 2013;76:145–54. DOI: 10.1016/j.neuroimage.2013.02.078

20. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019;18(5):439–58. DOI: 10.1016/S1474-4422(19)30034-1

21. Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. Stroke. 2007;38(11):3084–94. DOI: 10.1161/STROKEAHA.107.490193

22. Michinaga S, Koyama Y. Pathogenesis of brain edema and investigation into anti-edema drugs. International Journal of Molecular Sciences. 2015;16(5):9949–75. DOI: 10.3390/ijms16059949

23. Belov Kirdajova D, Kriska J, Tureckova J, Anderova M. Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells. Frontiers in Cellular Neuroscience. 2020;14(March):1–27. DOI: 10.3389/fncel.2020.00051

24. Shereen A, Nemkul N, Yang D, Adhami F, Dunn RS, Hazen ML, et al. Ex vivo diffusion tensor imaging and neuropathological correlation in a murine model of hypoxia-ischemia-induced thrombotic stroke. Journal of Cerebral Blood Flow and Metabolism. 2011;31(4):1155–69. DOI: 10.1038/jcbfm.2010.212

25. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 2003;20(3):1714–22. DOI: 10.1016/j.neuroimage.2003.07.005

26. Baron CA llan, Kate M, Gioia L, Butcher K, Emery D, Budde M, et al. Reduction of Diffusion-Weighted Imaging Contrast of Acute Ischemic Stroke at Short Diffusion Times. Stroke; a journal of cerebral circulation. 2015;46(8):2136–41. DOI: 10.1161/STROKEAHA.115.008815

27. Fu Y, Liu Q, Anrather J, Shi F dong. Immune interventions in stroke. Nat Rev Neurol. 2015;11(9):524–35. DOI: 10.1038/nrneurol.2015.144.Immune

28. Leinonen V, Vanninen R, Rauramaa T. Raised intracranial pressure and brain edema. 1st ed. Vol. 145, Handbook of Clinical Neurology. Elsevier B.V.; 2018. 25–37 p. DOI: 10.1016/B978-0-12-802395-2.00004-3

29. Budde MD, Janes L, Gold E, Turtzo LC, Frank JA. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: Validation in the rat using Fourier analysis of stained tissue sections. Brain. 2011;134(8):2248–60. DOI: 10.1093/brain/awr161

30. Simard J, Kent T, Chen M, Tarasov K, Gerzanich V. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. Lancet Neurol. 2007;6(3):258–68. DOI: Doi:10.1016/S1474-4422(07)70055-8. Brain

31. Anrather J, Iadecola C. Inflammation and Stroke: An Overview. Neurotherapeutics. 2016;13(4):661–70. DOI: 10.1007/s13311-016-0483-x

32. Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: Friend and foe for ischemic stroke. Journal of Neuroinflammation. 2019;16(1):1–24. DOI: 10.1186/s12974-019-1516-2

33. Wanner IB, Anderson MA, Song B, Levine J, Fernandez A, Gray-Thompson Z, et al. Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. Journal of Neuroscience. 2013;33(31):12870–86. DOI: 10.1523/JNEUROSCI.2121-13.2013

34. Adams KL, Gallo V. The diversity and disparity of the glial scar. Nature Neuroscience. 2018;21(1):9–15. DOI: 10.1038/s41593-017-0033-9

35. Ruiz F, Vigne S, Pot C. Resolution of inflammation during multiple sclerosis. Seminars in Immunopathology. 2019;41(6):711–26. DOI: 10.1007/s00281-019-00765-0

36. Carmichael ST, Kathirvelu B, Schweppe CA, Nie EH. Molecular, Cellular and Functional Events in Axonal Sprouting after Stroke. Exp Neurol. 2017;287(3):384–94. DOI: 10.1016/j.expneurol.2016.02.007.Molecular

37. Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. International Journal of Stroke. 2012;7(5):378–85. DOI: 10.1111/j.1747-4949.2012.00839.x

38. Li Y. Remyelination is critical for white matter stroke recovery. European Journal of BioMedical Research. 2015;1(4):18–22. DOI: Http://dx.doi.org/10.18088/ ejbmr.1.4.2015.pp18-22

39. Candelario-Jalil E. Injury and repair mechanisms in ischemic stroke: Considerations for the development of novel neurotherapeutics. Current Opinion in Investigational Drugs. 2009;10(7):644–54.

40. Dziewulska D, Mossakowski M. Cellular expression of tumor necrosis factor a and its receptors in human ischemic stroke. Clin Neuropathol. 2003;22(1):35–40.

41. Kliper E, Bashat D Ben, Bornstein NM, Shenhar-Tsarfaty S, Hallevi H, Auriel E, et al. Cognitive decline after stroke: Relation to inflammatory biomarkers and hippocampal volume. Stroke. 2013;44(5):1433–5. DOI: 10.1161/STROKEAHA.111.000536

42. Narasimhalu K, Lee J, Leong YL, Ma L, De Silva DA, Wong MC, et al. Inflammatory markers and their association with post stroke cognitive decline. International Journal of Stroke. 2015;10(4):513–8. DOI: 10.1111/ijs.12001

43. Shi K, Tian DC, Li ZG, Ducruet AF, Lawton MT, Shi FD. Global brain inflammation in stroke. The Lancet Neurology. 2019;18(11):1058–66. DOI: 10.1016/S1474-4422(19)30078-X

44. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. International Journal of Stroke. 2017;12(5):444–50. DOI: 10.1177/1747493017711816

45. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage. 2002; DOI: 10.1006/nimg.2002.1267

46. Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK. Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. Magnetic Resonance in Medicine. 2006;55(2):302–8. DOI: 10.1002/mrm.20774

47. Pitkonen M, Abo-Ramadan U, Marinkovic I, Pedrono E, Hasan KM, Strbian D, et al. Long-term evolution of diffusion tensor indices after temporary experimental ischemic stroke in rats. Brain Research. 2012;1445:103–10. DOI: 10.1016/j.brainres.2012.01.043

48. Nael K, Trouard TP, Lafleur SR, Krupinski EA, Salamon N, Kidwell CS. White matter ischemic changes in hyperacute ischemic stroke: Voxel-based analysis using diffusion tensor imaging and MR perfusion. Stroke. 2015;46(2):413–8. DOI: 10.1161/STROKEAHA.114.007000

49. Concha L. A macroscopic view of microstructure: Using diffusion-weighted images to infer damage, repair, and plasticity of white matter. Neuroscience. 2014;276:14–28. DOI: 10.1016/j.neuroscience.2013.09.004

50. Harris AD, Pereira RS, Mitchell JR, Hill MD, Sevick RJ, Frayne R. A comparison of images generated from diffusion-weighted and diffusion-tensor imaging data in hyper-acute stroke. Journal of Magnetic Resonance Imaging. 2004;20(2):193–200. DOI: 10.1002/jmri.20116

51. Bhagat YA, Hussain MS, Stobbe RW, Butcher KS, Emery DJ, Shuaib A, et al. Elevations of diffusion anisotropy are associated with hyper-acute stroke: a serial imaging study. Magnetic Resonance Imaging. 2008;26(5):683–93. DOI: 10.1016/j.mri.2008.01.015

52. Liu Y, D'Arceuil HE, Westmoreland S, He J, Duggan M, Gonzalez RG, et al. Serial diffusion tensor MRI after transient and permanent cerebral ischemia in nonhuman primates. Stroke. 2007;38(1):138–45. DOI: 10.1161/01.STR.0000252127.07428.9c

53. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion Tensor Imaging of the Brain. Neurotherapeutics. 2007;4(3):316–29. DOI: 10.1016/j.nurt.2007.05.011

54. Beaulieu C. The Biological Basis of Diffusion Anisotropy. Second Edi. Diffusion MRI: From Quantitative Measurement to In vivo Neuroanatomy: Second Edition. Elsevier; 2013. 155–183 p. DOI: 10.1016/B978-0-12-396460-1.00008-1

55. Pinter D, Gattringer T, Fandler-Höfler S, Kneihsl M, Eppinger S, Deutschmann H, et al. Early Progressive Changes in White Matter Integrity Are Associated with Stroke Recovery. Translational Stroke Research. 2020; DOI: 10.1007/s12975-020-00797-x

56. Cho AH, Sohn S Il, Han MK, Lee DH, Kim JS, Choi CG, et al. Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke: A preliminary report. Cerebrovascular Diseases. 2008;25(6):572–9. DOI: 10.1159/000132204

57. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T, Ville A, et al. Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. International Journal of Stroke. 2013;8(7):529–34. DOI: 10.1111/j.1747-4949.2012.00781.x

58. Battey TWK, Karki M, Singhal AB, Wu O, Sadaghiani S, Campbell BCV, et al. Brain edema predicts outcome after nonlacunar ischemic stroke. Stroke. 2014;45(12):3643–8. DOI: 10.1161/STROKEAHA.114.006884

59. Zhang X, Yan Y, Tong F, Li CX, Jones B, Wang S, et al. Progressive Assessment of Ischemic Injury to White Matter Using Diffusion Tensor Imaging: A Preliminary Study of a Macaque Model of Stroke. The Open Neuroimaging Journal. 2018;12(1):30–41. DOI: 10.2174/1874440001812010030

60. van Gelderen P, de Vleeschouwer MHM, DesPres D, Pekar J, van Zijl PCM, Moonen CTW. Water diffusion and acute stroke. Magnetic Resonance in Medicine. 1994;31(2):154–63. DOI: 10.1002/mrm.1910310209

61. Vargas ME, Barres BA. Why is Wallerian degeneration in the CNS so slow? Annual Review of Neuroscience. 2007;30:153–79. DOI: 10.1146/annurev.neuro.30.051606.094354

62. Albach FN, Brunecker P, Usnich T, Villringer K, Ebinger M, Fiebach JB, et al. Complete early reversal of diffusion-weighted imaging hyperintensities after ischemic stroke is mainly limited to small embolic lesions. Stroke. 2013;44(4):1043–8. DOI: 10.1161/STROKEAHA.111.676346

63. Tsai YH, Hsu LM, Weng HH, Lee MH, Yang JT, Lin CP. Functional diffusion map as an imaging predictor of functional outcome in patients with primary intracerebral haemorrhage. British Journal of Radiology. 2013;86(1021):1–8. DOI: 10.1259/bjr.20110644

64. Tipirneni-Sajja A, Christensen S, Straka M, Inoue M, Lansberg MG, Mlynash M, et al. Prediction of final infarct volume on subacute MRI by quantifying cerebral edema in ischemic stroke. Journal of Cerebral Blood Flow and Metabolism. 2017;37(8):3077–84. DOI: 10.1177/0271678X16683960

65. Broocks G, Faizy TD, Flottmann F, Schön G, Langner S, Fiehler J, et al. Subacute Infarct Volume with Edema Correction in Computed Tomography Is Equivalent to Final Infarct Volume after Ischemic Stroke: Improving the Comparability of Infarct Imaging Endpoints in Clinical Trials. Investigative Radiology. 2018;53(8):472–6. DOI: 10.1097/RLI.0000000000000475

66. Axer H, Gräßel D, Brämer D, Fitzek S, Kaiser WA, Witte OW, et al. Time course of diffusion imaging in acute brainstem infarcts. Journal of Magnetic Resonance Imaging. 2007;26(4):905–12. DOI: 10.1002/jmri.21088

67. Srivastava AK, Mehrotra G, Bhargava SK, Agarwal S, Tripathi RP. Studies on the time course of apparent diffusion coefficient and signal intensities on T2- and diffusion-weighted MR Imaging in acute cerebral ischemic stroke. J Med Phys. 2008;33(4):162–70. DOI: 10.4103/0971-6203.44479

68. Fragata I, Alves M, Papoila AL, Ferreira P, Nunes AP, Moreira NC, et al. Prediction of clinical outcome in subacute subarachnoid hemorrhage using diffusion tensor imaging. J Neurosurg. 2019;130(February):550–8. DOI: 10.3171/2017.10.JNS171793.550

69. Kimura-Ohba S, Yang Y, Thompson J, Kimura T, Salayandia VM, Cosse M, et al. Transient increase of fractional anisotropy in reversible vasogenic edema. Journal of Cerebral Blood Flow and Metabolism. 2016;36(10):1731–43. DOI: 10.1177/0271678X16630556

70. Ho ML, Rojas R, Eisenberg RL. Cerebral edema. American Journal of Roentgenology. 2012;199(3). DOI: 10.2214/AJR.11.8081

71. Nagaraja N, Forder JR, Warach S, Merino JG. Reversible diffusion-weighted imaging lesions in acute ischemic stroke: A systematic review. Neurology. 2020;94(13):571–87. DOI: 10.1212/WNL.0000000000009173

72. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. Annals of Neurology. 2000;47(4):462–9. DOI: 10.1002/1531-8249(200004)47:4<462::aid-ana9>3.3.co;2-p

73. Rivers CS, Wardlaw JM, Armitage PA, Bastin ME, Carpenter TK, Cvoro V, et al. Persistent infarct hyperintensity on diffusion-weighted imaging late after stroke indicates heterogeneous, delayed, infarct evolution. Stroke. 2006;37(6):1418–23. DOI: 10.1161/01.STR.0000221294.90068.c4

74. Ringer TM, Neumann-Haefelin T, Sobel RA, Moseley ME, Yenari MA. Reversal of early diffusion-weighted magnetic resonance imaging abnormalities does not necessarily reflect tissue salvage in experimental cerebral ischemia. Stroke. 2001;32(10):2362–9. DOI: 10.1161/hs1001.096058

75. Alia C, Spalletti C, Lai S, Panarese A, Lamola G, Bertolucci F, et al. Neuroplastic changes following brain ischemia and their contribution to stroke recovery: Novel approaches in neurorehabilitation. Frontiers in Cellular Neuroscience. 2017;11(March):1–22. DOI: 10.3389/fncel.2017.00076

76. Wardlaw JM, Chappell FM, Valdés Hernández MDC, Makin SDJ, Staals J, Shuler K, et al. White matter hyperintensity reduction and outcomes after minor stroke. Neurology. 2017;89(10):1003–10. DOI: 10.1212/WNL.0000000000004328

77. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. NeuroImage. 2012. DOI: 10.1016/j.neuroimage.2012.06.081

78. Visser MM, Yassi N, Campbell BCV, Desmond PM, Davis SM, Spratt N, et al. White Matter Degeneration after Ischemic Stroke: A Longitudinal Diffusion Tensor Imaging Study. Journal of Neuroimaging. 2019;29(1):111–8. DOI: 10.1111/jon.12556

79. Schirmer MD, Giese AK, Fotiadis P, Etherton MR, Cloonan L, Viswanathan A, et al. Spatial Signature of White Matter Hyperintensities in Stroke Patients. Frontiers in Neurology. 2019;10(March):1–10. DOI: 10.3389/fneur.2019.00208

80. Lee JK, Ko MH, Park SH, Kim GW. Prediction of Aphasia Severity in Patients with Stroke Using Diffusion Tensor Imaging. Brain Sci. 2021;11(304).

81. Lin LY, Ramsey L, Metcalf N v., Rengachary J, Shulman GL, Shimony JS, et al. Stronger prediction of motor recovery and outcome post-stroke by cortico-spinal tract integrity than functional connectivity. PLoS ONE. 2018;13(8):1–13. DOI: 10.1371/journal.pone.0202504

82. Moura LM, Luccas R, de Paiva JPQ, Amaro E, Leemans A, Leite C da C, et al. Diffusion tensor imaging biomarkers to predict motor outcomes in stroke: A narrative review. Frontiers in Neurology. 2019;10(MAY). DOI: 10.3389/fneur.2019.00445

83. Descoteaux M. High Angular Resolution Diffusion Imaging (HARDI). In: Webster JG, editor. Wiley Encyclopedia of Electrical and Electronics Engineering. Hoboken, NJ: Wiley; 2015. p. 1–25. DOI: 10.1002/047134608x.w8258

84. Theaud G, Houde JC, Boré A, Rheault F, Morency F, Descoteaux M. TractoFlow: A robust, efficient and reproducible diffusion MRI pipeline leveraging Nextflow & Singularity. Neuroimage. 2020;218(May). DOI: 10.1016/j.neuroimage.2020.116889

85. Boukadi M, Marcotte K, Bedetti C, Houde JC, Desautels A, Deslauriers-Gauthier S, et al. Test-retest reliability of diffusion measures extracted along white matter language fiber bundles using HARDI-based tractography. Frontiers in Neuroscience. 2019;12:1055. DOI: 10.3389/fnins.2018.01055

86. Moffat BA, Chenevert TL, Meyer CR, Mckeevery PE, Hall DE, Hoff BA, et al. The functional diffusion map: An imaging biomarker for the early prediction of cancer treatment outcome. Neoplasia. 2006;8(4):259–67. DOI: 10.1593/neo.05844

87. Borich MR, Mackay AL, Vavasour IM, Rauscher A, Boyd LA. NeuroImage : Clinical Evaluation of white matter myelin water fraction in chronic stroke. NeuroImage: Clinical [Internet]. 2013;2:569–80. DOI: 10.1016/j.nicl.2013.04.006

88. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, et al. Aortic Stiffness, increased white matter free water and altered microstructural integrity: a continuum of injury. Stroke. 2017;48(6):1567–73. DOI: 10.1161/STROKEAHA.116.016321.Aortic

89. Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, et al. Evidence-based guideline: The role of diffusion and perfusion mri for the diagnosis of acute ischemic stroke: Report of the therapeutics and technology subcommittee of the American Academy of Neurology. Neurology. 2010;75:175–85. DOI: 10.1212/WNL.0b013e318219a0b4