

Developmental trajectory of the prefrontal cortex: a systematic review of diffusion tensor imaging studies

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Abstract Fluctuations in gray and white matter volumes in addition to the fibers' reorganization and refinement of synaptic connectivity apparently happen in a particular tempo-spatial sequence during the dynamic and prolonged process of cerebral maturation. These developmental events are associated with regional modifications of brain tissues and neural circuits, contributing to networks' specialization and enhanced cognitive processing. According to several studies, improvements in cognitive processes are possibly myelin-dependent and associated to white matter maturation. Of particular interest is the developmental pattern of the prefrontal cortex (PFC), more specifically the PFC white matter, due to its role in high-level executive processes such as attention, working memory and inhibitory control. A systematic review of the literature was conducted using the Web of Science, PubMed and Embase databases to analyze the development of PFC white matter using Diffusion Tensor Imaging (DTI), a widely used non-invasive technique to assess white matter maturation. Both the research and

reporting of results were based on Cochrane's recommendations and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Information extracted from 27 published studies revealed an increased myelination, organization and integrity of frontal white matter with age, as revealed by DTI indexes (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD] and axial diffusivity [AD]). These patterns highlight the extended developmental course of the frontal structural connectivity, which parallels the improvements in higher-level cognitive functions observed between adolescence and early adulthood.

Keywords Prefrontal cortex · White matter · Myelination · Diffusion tensor imaging · Development

Introduction

Several studies assessed white matter maturation through non-invasive imaging techniques such as DTI. This technique has become popular considering its sensitivity in evaluating axons' features, using the random motion of water molecules known as thermal Brownian motion (Hagmann et al. 2006; Le Bihan 2003; Thomason and Thompson 2011). This random motion of water molecules is essential to the accuracy of DTI and therefore deserves a detailed explanation of its underlying mechanism. The random displacement observed in biological tissues, seems to be driven by its anatomical architecture, and dependent on the histological properties of tissues such as cell membranes, myelin sheaths and molecules (Hagmann et al. 2006; Mori and Zhang 2006). In this sense, water diffusion within a specific milieu might be classified as isotropic—water molecules travel randomly in all directions,

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or anisotropic—water molecules get displaced into a specific direction (Hagmann et al. 2006; Thomason and Thompson 2011). Once water molecules spread around more freely, the micromotion of the water molecules in gray matter (GM) is considered isotropic. This process is associated to the less fibrillar and intricate nature of GM, when compared to the white matter. In the healthy white matter this process is different and the movement of water molecules is essentially considered anisotropic, or in other words, water molecules travel along a preferred direction, guided by structural barriers such as glial cells, axonal membranes and myelin bundles, present in white matter (Beaulieu 2002; Hagmann et al. 2006; Pierpaoli et al. 1996).

Diffusion-weighted image (DWI) acquisition consists in the application of a gradient sequence within a commonly used range of 700–1300 s/mm², values that might change depending on the acquisition protocol. This sequence is applied to the entire brain covering a minimum of six directions in the X, Y and Z axes, in addition to an image with no gradient ($b=0$ s/mm²) at least (Alexander et al. 2007; Alger 2012; Chilla et al. 2015; Nishikawa et al. 2013). The b_0 image (s) is used to compare the behavior of the water molecules between its initial state, when no gradient was yet applied, and after gradients' application. To estimate the diffusion values from each voxel of the acquired DWI, the eigenvectors and the eigenvalues need to be determined. The main directions of diffusivity or eigenvectors result from estimating the diffusion along three orthogonal directions. The eigenvalues are the diffusion values associated to each main direction. Once determined, the eigenvectors and eigenvalues describe the properties of the diffusion tensor (Hagmann et al. 2006; Le Bihan et al. 2001). The classification of the eigenvalues is as follows, $\lambda_1 \geq \lambda_2 \geq \lambda_3$, and each one matches one eigenvector. The eigenvector that corresponds to the largest eigenvalue (λ_1) represents the principal direction of the diffusion. The diffusion transversal to the main direction is represented by λ_2 and λ_3 . The relation between the eigenvalues reveals the diffusion properties within a specific image. If the eigenvalues significantly change from each other, diffusion is assumed to be anisotropic, but if all the eigenvalues are similar, diffusion is presumed to be isotropic. Once the diffusion tensor is obtained, the scalar indexes representing the mean diffusivity and anisotropy within a specific voxel may be calculated.

Several diffusivity-based measures are referred in the DTI research field, however fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) seem to be the most widely used. The values extracted through these indexes are associated with the motion of water molecules in brain tissues (Alexander et al. 2007; Alger 2012; Hagmann et al. 2006; Le Bihan et al. 2001; Mori and Zhang 2006; Pierpaoli et al. 1996). Specifically, if

the relation between the eigenvalues assumes an elongated ellipsoid shape, the diffusion of water is assumed to be anisotropic, as represented by the FA index.

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

FA is a scalar measure of the magnitude of diffusion anisotropy in a voxel, derived from a ratio of the principal diffusivities. Basically, this measure is computed through the comparison of each eigenvalue ($\lambda_1, \lambda_2, \lambda_3$) with the diffusion coefficient (D). FA represents the degree in which the diffusion of water molecules is anisotropic or unidirectional. The value of FA representing this motion of water molecules into a preferred direction varies between 0 and 1. Zero represents isotropic diffusion of water molecules with no directional preference, and 1 represents the unidirectional displacement of water molecules or anisotropy.

A second largely used measure is MD, which derives from the mean of the three eigenvalues $(\lambda_1 + \lambda_2 + \lambda_3)/3$, and indicates the overall displacement of water molecules in a voxel, although not providing information about the direction of the movement. Two additional, although less referred in the literature as FA and MD indexes, are AD and RD. AD is derived from the largest of the three eigenvalues (λ_1) in the Z or longitudinal axis. This index represents the rate of water diffusion in the direction of greatest diffusion. The greatest diffusion in white matter is usually considered to be parallel to the axonal tracts. RD derives from the average of the second λ_2 and third λ_3 eigenvalues in the X and Y-axes, representing the diffusion perpendicular to the fiber direction. The diffusion of water molecules perpendicular to the main direction of fibers is usually lower than the diffusion parallel to fibers' orientation (Alexander et al. 2007; Alger 2012; Hagmann et al. 2006; Le Bihan et al. 2001; Mori and Zhang 2006; Pierpaoli and Basser 1996; Thomason and Thompson 2011). A great advantage of DTI is providing rotationally-invariant diffusivity measures, independent of the position of the fibers in space or how the subjects' head was positioned in the scan (Alexander et al. 2007; Alger 2012).

Several methods are used to analyze DTI data. Voxelwise and tract-based spatial statistics (TBSS) are both whole-brain fully automated voxel-based approaches. Voxelwise analysis runs in SPM allowing comparing group means using a Univariate approach in which each voxel is processed separately. TBSS runs in FSL and analyze all the tracts of the brain, comparing each subject to a group mean skeleton derived from a center value of each tract (Smith et al. 2006). Diffusion tensor tractography (DTT) allows the reconstruction of white matter bundles using the diffusion tensor of each voxel. Finally, the region of interest (ROI) method is

used to assess regions defined à priori by the researcher and the retrieved mean values are compared between subjects (Mukherjee et al. 2008; Froeling et al. 2016).

Interpreting the DTI indexes in the light of brain maturation is not straightforward, however it seems that these water diffusion related measures effectively change during development reflecting underlying tissues' structural changes (Neil et al. 2002). In this sense, some assumptions regarding the hypothetical associations between diffusivity measures and biological mechanisms have been referred in the literature. Commonly anisotropy is associated to the architecture of the white matter myelinated fibers and increased myelination. High values of FA have been associated with enhanced neural connectivity, white matter packing, greater fiber integrity and myelination. Although the presence of myelin is not a key factor for anisotropic diffusion to exist, it may modulate the degree of anisotropy (Beaulieu 2002). In fact, it seems that myelin depletion or damaged myelin significantly changes the measures of anisotropy (Assaf and Pasternak 2008). Specifically, the degree of anisotropic diffusion apparently rises along the neurodevelopmental process of myelination; whereas, reporting from myelin-related disorders such as Multiple Sclerosis (MS) (Preziosa et al. 2017; Roosendaal et al. 2009) or Wallerian degeneration (Xie et al. 2011), decreased anisotropic values are possibly associated to damaged myelin (Neil et al. 2002). As such, changes in FA may detect rapid microstructural changes in the brain such as neuronal plasticity, axonal structure remodeling, fiber density and reorganization (Ding et al. 2013) and activity-dependent myelination mechanisms (Scholz et al. 2009).

While myelination does not appear to be a condition to significantly change FA, it may be important in detecting alterations in MD. It has been observed that the absence of myelin prompts the water displacement to be greater in the perpendicular direction to the axonal bundles, than in the parallel direction (main axis), increasing thus the MD values (Beaulieu 2002). Hence, increased MD values seem to be associated with myelin lesions; whereas low MD values have been associated with white matter integrity since it reflects diminished free diffusion within tissues (Preziosa et al. 2017).

Regarding the AD, this index is thought to reflect the integrity/damage of axons. It has been shown that obstructions to parallel diffusion seem to increase from the breakdown of the longitudinal axonal structure (Beaulieu 2002). In this sense, high AD values have been associated with intact healthy axons and low AD values have been linked to injured axons (Beaulieu 2002) as, for example, in Wallerian degeneration (Sun et al. 2008).

Finally, the RD appears to be associated with myelination/demyelination processes (Song et al. 2003; Sun et al. 2006). In fact, it seems that the diffusion perpendicular to the

axonal tracts is constrained by the interactions of the water molecules with cellular membranes and myelin sheaths. This constriction is possibly causing diffusion to become hindered once water molecules do not move freely in the presence of obstacles (Alexander et al. 2007; Medana and Esiri 2003; Thomason and Thompson 2011). Thus, while transverse diffusivity is diminished in healthy tissues, it seems to increase in the presence of injured axons as in MS and Wallerian degeneration (Roosendaal et al. 2009; Sun et al. 2008; Xie et al. 2011).

According to neuroimaging findings, the human brain presents a specific maturing schedule throughout life. This particular neurodevelopmental timing seems to be related to progressive and regressive neurobiological events that occur at specific ages, reflecting a dynamic and extended developmental process both in terms of structure and cognitive functioning (Giedd 2004; Lenroot and Giedd 2006). Fluctuations of gray and white matter, as measured through morphometric indexes such as volume and cortical thickness, and the reorganization and refinement of synaptic connectivity apparently happen in a particular temporo-spatial sequence since birth until early adulthood, and are associated to regional modifications of brain tissues and neural circuits (Durstun et al. 2001; Giedd and Rapoport 2010; Giedd et al. 1999; Giedd 2008; Huttenlocher 1979; Shaw et al. 2008). Accordingly, these findings suggest that particular structural and functional characteristics arise along brain development, eventually showing interdependency with specific cognitive milestones (Bennett et al. 1964; Casey et al. 2000; Paus et al. 1999; Schmithorst et al. 2005).

Specifically, a major increase of global gray matter (GM) is observed during childhood possibly associated to a high rate of synapse production, and is followed by a decline throughout adolescence (Durstun et al. 2001; Giedd et al. 1999; Giedd 2004; Gogtay et al. 2004) This GM thinning during adolescence, which is associated to pruning, among other cellular maturational processes, has been associated to the networks' specialization (Giedd 2004; Lenroot and Giedd 2006; Petanjek et al. 2011) and to improved cognitive skills. This process of GM pruning seems to occur in the frontal lobes between adolescence and early adulthood (Durstun et al. 2001; Giedd et al. 1999; Giedd 2004; Gogtay et al. 2004; Lebel and Beaulieu 2011; Lenroot and Giedd 2006; Petanjek et al. 2011).

On the other hand, whole brain white matter generally increases throughout life, fact associated with the growing need of additional and effective inter-neuronal connections to sustain the increasing central nervous system (CNS) complexity (Bennett et al. 1964; Dubois et al. 2013; Durstun et al. 2001; Giedd et al. 1999; Giedd 2004; Lenroot and Giedd 2006; Snaidero and Simons 2014).

Myelin, the major white matter compound, enfolds axons and basically acts as an electrical insulator that speeds

impulse conduction between neurons and increases brain efficiency (Fields 2005, 2008; Snaidero and Simons 2014). The process of axons' myelination during brain development seems to be region-specific, eventually following a specific temporal sequence during the CNS maturation. This axonal myelination process seems to underlie the interaction between brain structure and environmental factors, which conversely modulate brain functioning (Dubois et al. 2013; Fields 2005; Snaidero and Simons 2014).

Actually, it seems that the major myelin formation is an on-going process during the first three to four decades of the human lifecycle, following an inferior to superior and posterior-to-anterior (Colby et al. 2011; Paus 2010) and central-to-peripheral direction of maturation (Dubois et al. 2013; Snaidero and Simons 2014). Specifically, myelination is first observed in the dorsal sensorimotor areas (temporo-occipital and parieto-frontal areas) while more time is needed for the temporo-parietal and frontal association areas to be fully myelinated, probably due to its relation with complex cognitive processes (Deoni et al. 2011; Dubois et al. 2013; Gogtay et al. 2004; Lenroot and Giedd 2006; Paus et al. 2001). Specifically, the prefrontal cortex (PFC) maturation, including the dorsolateral PFC and orbitofrontal PFC, which is not finished before the second decade of life (Giedd 2004; Gogtay et al. 2004) progresses from a posterior to anterior direction (Colby et al. 2011; Gogtay et al. 2004) with the most caudal areas maturing earlier than the rostral ones (Tames et al. 2010).

Additionally, the PFC maturational processes, including the major frontal tracts (superior longitudinal fasciculus; inferior fronto-occipital fasciculus; and uncinate fasciculus) are likely to be associated with the PFC functional role in supporting high-level cognitive functions such as attentional processing, working memory and inhibitory control (Kraus et al. 2007; Martino et al. 2013) suggesting that frontal white matter maturation might be the most relevant neural substrate of improved executive processes.

Finally, changes in white matter organization have been broadly observed, *in vivo*, through diffusion tensor imaging (DTI) metrics, which are believed to be quite sensitive to myelin changes, providing insight into subtle microstructural alterations (e.g. axons' myelination or demyelination; axonal injury or degeneration; axonal packing), whether these alterations happen during the healthy developmental pathway of the brain or due to clinical conditions (e.g. multiple sclerosis (MS), Wallerian degeneration) (Aung et al. 2013; Fox et al. 2011; Le Bihan et al. 2001; Song et al. 2003; Sun et al. 2006; Xie et al. 2011). Once DTI provides information about axonal organization and integrity of neural pathways that ensure communication among several regions of the brain, which could not be retrieved from standard MRI measures (e.g. volumes or cortical thickness), it may provide relevant findings about PFC white matter developmental course.

Therefore, the main purpose of the present review was to systematize current knowledge, on the developmental pathway of the frontal cortex in terms of its microstructural connectivity, as shown by DTI metrics, using the PRISMA guidelines - <http://www.prisma-statement.org> - (Moher et al. 2009).

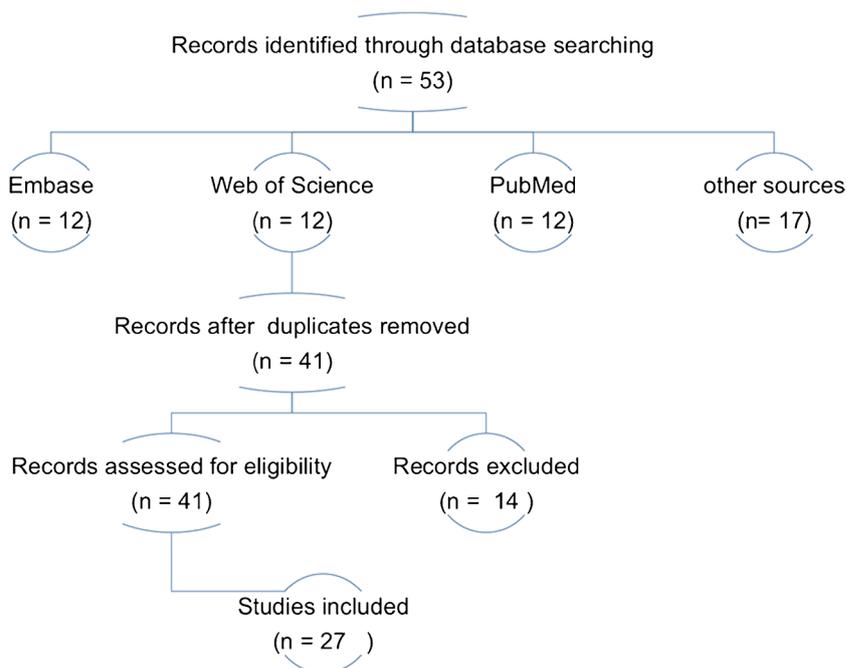
Methods

A search in peer-review publications was performed in March 2017 using the Web of Science, PubMed and Embase databases to identify relevant papers that evaluated the development of the frontal white matter in healthy individuals, using DTI. A total of 53 articles were identified through database searching. Records were retrieved using the key-expressions: (“Diffusion tensor” OR “DTI”) AND (typical OR normal OR healthy) AND (brain development AND “white matter” AND frontal). In detail, the search through Embase database was performed as follows: advanced search in “Journals”, in the fields of Neuroscience and Medicine, using the “key-expressions” in all fields, open access articles, short communications and articles in press; search through Web of Science and PubMed was performed using the “key-expressions”. No time restriction was applied. Additional articles that were referenced in other studies were also assessed. In order to pursue the database searching and the assessment for eligibility some inclusion and exclusion criteria were formerly defined. Specifically, articles were included if: 1) were published in a peer-review journal; 2) assessed the frontal white matter development in healthy subjects employing cross-sectional or longitudinal designs; 3) used DWI acquisitions and DTI measures; 4) evaluated one or more out of the four DTI indexes: FA, MD, AD and RD; 5) were written in English. As exclusion criteria was established: 1) research using clinical samples; 2) studies correlating DTI measures with clinical variables; 3) other imaging method that was not DTI; 4) and aging studies including only adults (> 40 years old). After a careful selection of 53 studies, 12 duplicates were removed, 41 were assessed for eligibility and only 27 articles were included in this systematic review (see the diagram in Fig. 1).

Table 1 lists all the articles revised and provides the first author, year of publication, as well as brief information concerning the participants enrolled in the study in addition to details related to the methodology, regions of interest, DTI indexes, main results and statistical analyses.

Results

Overall, the data gathered in this systematic review document a growing of FA over the distinct periods of

Fig. 1 Flow diagram for paper selection

development, concomitant with a reduction of MD and RD and to a lesser extent AD, in the frontal cortex and in its main association tracts. The findings disclosed by the analysis of the DTI indexes in healthy individuals, from neonatal ages until adulthood, suggested a late process of frontal white matter maturing, which still remains in progress throughout the third decade of life.

The majority of the studies that evaluated the FA index in the frontal white matter showed a linear anisotropic increase with age, since the neonatal period until early adulthood (range: birth–30 years), being the lowest FA values observed in children and the highest in young adults (Colby et al. 2011; Schneider et al. 2004; Simmonds et al. 2014). Studies comparing distinct age groups reported that children (range: 8–13) showed the lowest FA values in comparison to older adolescents (range: 16–18) or young adults (range: 18–31, Klingberg et al. 1999; Qiu et al. 2008, 2010), yet no FA changes were observed between younger (range: 6–8) and older children (range: 9–11, Qiu et al. 2008). Additionally, no significant correlations were found between age and FA values in a cohort ranging in age between 5 and 19 years old (Bonekamp et al. 2007).

In terms of the diffusivity measures (MD, RD and AD) more variability was observed among studies. In relation to MD, most of the studies that assessed this index showed similar results, i.e. decreasing MD with age (range: 5–43, Bartzokis et al. 2012; Bonekamp et al. 2007; Qiu et al. 2008, 2010) and the greatest trough was observed around 43 years old (Bartzokis et al. 2012); although, a previous study found that infants (range: 24–36 months) displayed similar MD to adults (Schneider et al. 2004).

Regarding the RD and AD indexes, the findings revealed an overall decline with age (range: 6–54, Bartzokis et al. 2012; Kumar et al. 2012; Qiu et al. 2008; Simmonds et al. 2014), with the maximum being observed at approximately 35 years old for RD and at age 54 for AD (Bartzokis et al. 2012); whereas, decreased RD but no changes in AD over age (range: 5–28) were observed in the study conducted by Colby et al. (2011).

In the analysis of specific frontal regions—the superior, the middle and the inferior frontal gyri, the dorsolateral and the orbitofrontal cortex—has emerged a pattern of increasing anisotropy and decreasing diffusivity levels along the distinct developmental periods. FA levels were observed to increase with age between the postnatal ages and early adulthood in the superior frontal gyrus (range: 21 days–27 years, Lobel et al. 2009; Moon et al. 2011; Snook et al. 2005; Tamnes et al. 2010), in the middle frontal gyrus (range: 6–35, Barnea-Goraly et al. 2005; Li and Noseworthy 2002; Tamnes et al. 2010), in the inferior frontal gyrus (range: 21 days–30 years, Ashtari et al. 2007; Barnea-Goraly et al. 2005; Lobel et al. 2009; Tamnes et al. 2010), in the dorsolateral, and in the orbitofrontal cortex (range: 6–30, Barnea-Goraly et al. 2005; Tamnes et al. 2010). Overall, the studies documented that adults displayed the highest FA levels whether compared with adolescents or children or infants.

Considering the diffusivity indexes MD, RD and AD, a trend for values to decrease with age was observed in the superior frontal gyrus (range: 21 days–30 years, Lobel et al. 2009; Moon et al. 2011; Snook et al. 2005; Tamnes et al. 2010), in the middle frontal gyrus (range: 8–30, Tamnes et al. 2010), in the inferior frontal gyrus

Table 1 Lists the revised articles with key information about the authors, year of publication, sample size, age range, design, method, regions of interest, DTI indices, main results and statistics

Study	N	Age ranges	Design	Method of analysis	DTI indices	ROI	Results	Statistics
Asato et al. 2010	114	8–12 ($n=36$); 13–17 ($n=45$); 18–28 ($n=33$); mean age: 15.5 ± 4.49	Transversal	TBSS	RD	sLF; iFOF; UF	↓RD, plateau end of adolescence in sLF+iFOF	One-way ANOVA
Ashtari et al. 2007	24 (all males)	10–16 ($n=12$); 17–20 ($n=12$); mean age: 16.6 ± 2.5	Transversal	Voxelwise	FA, MD, RD, AD	IFG	↑FA, ↑AD No differences in RD, MD	Voxelwise ANCOVA
Barnea-Goraly et al. 2005	34 (18 male)	6–19; mean age: 12.7 ± 3.3	Transversal	Voxelwise	FA	DLPFC; OFC; MFG; IFG	↑FA	Linear regression
Bartzokis et al. 2012	171 (93 male)	14–93; mean age: 51 ± 22	Transversal	ROI	FA, MD, RD, AD	FWM	↓RD, MD, AD	Pearson correlation
Bava et al. 2010	22 (15 male)	Time 1: 16–20 (mean age: 17.8 ± 1.4); Time 2: 17–21 (mean age: 19.2 ± 1.4)	Longitudinal	TBSS	FA, MD, RD, AD	iFOF; sLF	sLF: ↑FA, ↓MD, ↓RD; Right iFOF: ↑MD, ↑AD; Left iFOF: ↓MD, ↓AD	t-tests
Bonekamp et al. 2007	40 (22 male)	5–19; mean age: 13.7 ± 3.5	Transversal	ROI	FA, MD	FWM; sLF; sFOF	FWM+sLF: ↓MD sFOF: ↑FA ↓MD	Univariate GLM
Colby et al. 2011	32 (16 male)	5–28; mean age: 14.4 ± 7.2	Transversal	TBSS	FA, AD, RD	FWM	↑FA, ↓RD, no changes in AD	Regression
Eluvathingal et al. 2007	31 (15 male)	6–17; mean age: 11.4 ± 3.1	Transversal	DTT	FA, MD, AD, RD	iFOF; UF	↑FA, ↓MD, ↓AD, ↓RD	Pearson correlation
Giorgio et al. 2008	62 (33 male)	13.5–21 ($n=42$); 23–42 ($n=20$)	Transversal	TBSS	FA	Right sLF	↑FA in adults	Pearson correlation
Klingberg et al. 1999	12	8–12 ($n=7$); 20–31 ($n=5$)	Transversal	ROI	FA	FWM	↑FA	–
Krogsrud et al. 2016	159 (69 male)	Time 1: 4–9 (mean age: 6.2 ± 1.1); Time 2: 5–11 (mean age: 7.8 ± 1.1)	Longitudinal	TBSS	FA, MD, AD, RD	iFOF; sFOF; sLF; UF	↑FA, ↓MD, ↓RD; ↓AD in the sLF only	GLM, Correlation, t-tests
Kumar et al. 2012	30 (18 male)	8–24; mean age: 17.7 ± 4.6	Transversal	ROI	AD, RD	FWM	↓AD, ↓RD	Pearson correlation
Lebel and Beaulieu 2011	103 (51 male)	5–32; mean age: 14.8 ± 6.4	Longitudinal	DTT	FA, MD, RD, AD	sLF; sFOF; iFOF; UF	↑FA, ↓MD; ↓RD; ↓AD in younger subjects; ↑AD in adolescents and adults	Linear mixed models
Lebel et al. 2008	202 (104 male)	5–29; mean age: 15.2 ± 6.1	Transversal	ROI/DTT	FA, MD	iFOF; sFOF; sLF; UF	↑FA, ↓MD	Regression

Table 1 (continued)

Study	N	Age ranges	Design	Method of analysis	DTI indices	ROI	Results	Statistics
Li and Noseworthy 2002	16	13–15 (mean age: 14); 22–35 (mean age: 36)	Transversal	Voxelwise	FA	MFG	↑FA	t-tests
Lobel et al. 2009	72	3 weeks–19 years	Transversal	ROI	FA, MD	SFG; IFG	↑FA, ↓MD	Spearman correlation
Moon et al. 2011	87 (37 male)	4–17; mean age: 11.2 ± 3.6	Transversal	ROI	FA, MD	SFG	↑FA, ↓MD	Linear regression
Muftuler et al. 2012	126 (67 male)	6–11; mean age: 8.1 ± 1.3	Transversal	TBSS	FA, MD	iFOF; sLF; UF	↑FA, ↓MD	GLM
Qiu et al. 2008	75 (40 male)	6–8 (n = 24, mean age: 7.4 ± 0.3); 9–11 (n = 27, mean age: 10.3 ± 0.5); 18–26 (n = 24, mean age: 22.8 ± 2.3)	Transversal	TBSS/ROI	FA, MD, RD, AD	FWM	↑FA (older children vs adults), ↓MD, ↓RD, ↓AD	ANOVA
Qiu et al. 2010	92 (42 male)	11–13 (n = 32); 16–18 (n = 32); 23–25 (n = 28)	Transversal	Voxel based	FA, MD	FWM	↑FA, ↓MD	Linear correlation + t-test
Schneider et al. 2004	52 (30 male)	Birth – 16 (mean age: 6.6)	Transversal	ROI	MD, FA	FWM	↓MD, ↑FA	Multieponential regression
Simmonds et al. 2014	128 (61 male)	8–29; mean age: 14.9 ± 4.2	Longitudinal	TBSS	FA, AD, RD	FWM; sFOF; sLF; UF	↓FA, ↓RD, ↓AD; ↑AD in UF	Mixed-effects regression
Snook et al. 2005	60 (28 male)	8–12 (n = 32, mean age: 11.1 ± 1.3); 21–27 (n = 28, mean age: 24.4 ± 1.8)	Transversal	ROI	FA, MD	SFG	↑FA, ↓MD	Linear regression + t-tests
Snook et al. 2007	60 (28 male)	8–12 (n = 32, mean age: 11.1 ± 1.3); 21–27 (n = 28, mean age: 24.4 ± 1.8)	Transversal	ROI, Voxel based	FA, MD	sLF; sFOF	↑FA, ↓MD	Linear regression + t-tests
Taki et al. 2013	246 (119 male)	5–18	Transversal	Voxel based ROI	FA, MD	sLF; UF; iFOF	↑FA, ↓MD	Correlation
Tammes et al. 2010	168 (81 male)	8–30; mean age: 17.7 ± 6.1	Transversal	ROI	FA, MD, AD, RD	SFG; MFG; IFG; OFC	↑FA, ↓MD, ↓RD, ↓AD	Regression
Uda et al. 2015	52 (33 male)	2 months–25 years; mean age: 105.8 ± 82.9 months	Transversal	ROI	FA, MD, AD, RD	sLF	↑FA, ↓MD, ↓AD, ↓RD	Regression ANOVA

AD Axial diffusivity, *DLPCF* Dorsolateral prefrontal cortex, *DTT* Diffusion tensor tractography, *FA* Fractional anisotropy, *FWM* Frontal white matter, *IFG* Inferior frontal gyrus, *iFOF* Inferior fronto-occipital fasciculus, *MD* Mean diffusivity, *MFG* Middle frontal gyrus, *OFC* Orbitofrontal cortex, *RD* Radial diffusivity, *ROI* Region of interest, *SFG* Superior frontal gyrus, *sFOF* Superior fronto-occipital fasciculus, *sLF* Superior longitudinal fasciculus, *TBSS* Tract-based spatial statistics, *UF* Uncinate fasciculus

(21 days–30 years, Lobel et al. 2009; Tamnes et al. 2010) and in the orbitofrontal cortex (range: 8–30, Tamnes et al. 2010). Overall, all studies but one (Ashtari et al. 2007) documented that adult individuals displayed the lowest diffusivity levels (MD, RD or AD) when compared with adolescents or children or infants. Specifically, Ashtari et al. (2007) found an augmentation of AD without significant changes in RD and MD in the inferior frontal gyrus of older adolescents (range: 17–20) compared to their young peers (range: 10–16).

A tendency to an increased FA and decreased MD and RD as a function of age was also observed in the frontal association tracts, but not so consistent were the results for AD. Specifically, increased FA with age was observed since early ages until adulthood in the inferior fronto-occipital fasciculus (range: 4–30, Elovathingal et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Taki et al. 2013), in the superior fronto-occipital fasciculus (range: 4–30, Bonekamp et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Snook et al. 2007; Simmonds et al. 2014), in the superior longitudinal fasciculus (range: 2 months–42 years, Bava et al. 2010; Giorgio et al. 2008; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Snook et al. 2007; Simmonds et al. 2014; Taki et al. 2013; Uda et al. 2015) and in the uncinate fasciculus (range: 4–30, Elovathingal et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Simmonds et al. 2014; Taki et al. 2013). Conversely, no age-related changes in the FA values were found between childhood and late adolescence (range: 5–19) in the superior longitudinal fasciculus (Bonekamp et al. 2007) and between late-adolescence and early-adulthood (range: 16–21) in the inferior fronto-occipital fasciculus (Bava et al. 2010).

Concerning the diffusivity measures observed in the association tracts, the findings were not so consistent among studies, especially in relation to the rate of change of RD and AD with age. Specifically, decreased MD values across age in the inferior fronto-occipital fasciculus were found by nearly all the studies included in this review (range: 4–30, Elovathingal et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Taki et al. 2013), excluding the one of Bava et al. (2010), which found inter-hemispheric variations. Likewise, decreasing MD was found in the superior fronto-occipital fasciculus (range: 4–30, Bonekamp et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Snook et al. 2007), in the superior longitudinal fasciculus (range: 2 months–30 years, Bava et al. 2010; Bonekamp et al. 2007; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Snook et al. 2007; Taki et al. 2013; Uda et al. 2015) and in the uncinate fasciculus (range: 4–30, Elovathingal et al. 2007; Krogsrud et al. 2016; Lebel

and Beaulieu 2011; Lebel et al. 2008; Muftuler et al. 2012; Taki et al. 2013).

A reduction of RD with age was observed in the inferior fronto-occipital fasciculus (range: 4–30, Asato et al. 2010; Elovathingal et al. 2007; Krogsrud et al. 2016), in the superior fronto-occipital fasciculus (range: 4–30, Krogsrud et al. 2016; Simmonds et al. 2014), in the superior longitudinal fasciculus (range: 2 months–30 years, Asato et al. 2010; Bava et al. 2010; Krogsrud et al. 2016; Simmonds et al. 2014; Uda et al. 2015) and in the uncinate fasciculus (range: 4–30, Asato et al. 2010; Elovathingal et al. 2007; Krogsrud et al. 2016; Simmonds et al. 2014). Contrarily, no changes in RD values were observed between late-adolescent individuals and early-adults (range: 14–32, Bava et al. 2010; Lebel and Beaulieu 2011) in the inferior fronto-occipital fasciculus, superior fronto-occipital fasciculus, superior longitudinal fasciculus, and uncinate fasciculus.

Regarding AD, reduced values across age were found in the inferior fronto-occipital fasciculus (range: 5–17, Elovathingal et al. 2007; Lebel and Beaulieu 2011), in the superior fronto-occipital fasciculus (range: 8–29, Simmonds et al. 2014), in the superior longitudinal fasciculus (range: 2 months–30 years, Lebel and Beaulieu 2011; Simmonds et al. 2014; Uda et al. 2015), and in the uncinate fasciculus (range: 4–14, Krogsrud et al. 2016; Lebel and Beaulieu 2011); differently, increased AD (range: 8–32) was found in the uncinate fasciculus (Lebel and Beaulieu 2011; Simmonds et al. 2014) and in the inferior fronto-occipital fasciculus and superior longitudinal fasciculus (range: 14–32, Lebel and Beaulieu 2011). However, no changes in AD were observed between childhood (range: 4–9) and early adolescence (range: 5–11) in the inferior fronto-occipital fasciculus (Krogsrud et al. 2016).

Additionally, inter-hemispheric variances were observed in the inferior fronto-occipital fasciculus. Increased MD and AD were found in the right inferior fronto-occipital fasciculus while both measures were reduced in the left inferior fronto-occipital fasciculus (Bava et al. 2010).

Distinct maturation timings have also been observed in some of the prefrontal tracts. Specifically, non-linear maturation trajectories (increased FA, and decreased MD and RD) were found in the inferior fronto-occipital fasciculus and in the superior fronto-occipital fasciculus. The maturation trajectory of the inferior fronto-occipital fasciculus was illustrated by an exponential growth curve that peaked at the end of the adolescence, and reached a plateau during early adulthood (Bava et al. 2010; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008). The maturation of the superior fronto-occipital fasciculus, as revealed by increased FA and decreased RD and AD, was attained in early adolescence (Krogsrud et al. 2016; Lebel and Beaulieu 2011; Simmonds et al. 2014). An exponential curve of maturation was also observed in the

superior longitudinal fasciculus, as revealed by increased FA, and decreased MD, RD and AD. The maturational peak was found during adolescence and the plateau was reached throughout early adulthood (Bava et al. 2010; Krogsrud et al. 2016; Lebel and Beaulieu 2011; Lebel et al. 2008; Simmonds et al. 2014); however, another study had found a linear growth of the right superior longitudinal fasciculus FA in young adults (range: 23 to 42, Giorgio et al. 2008). Considering the developmental course of the uncinate fasciculus, it was observed to continue beyond the age 28, as measured through increased FA and AD, and decreased MD; however in relation to RD, it was fully matured at early adolescence (range: 11–13), (Krogsrud et al. 2016; Lebel and Beaulieu 2011; Simmonds et al. 2014). Yet, one study had revealed a linear developmental trajectory of FA until age 25 (Lebel et al. 2008). In accordance, Muftuler et al. (2012) have found that the lowest rate of change of FA and MD, approximately 0.5 to 1% per year, measured in the inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus, is observed in youth (age range: 6–11). Furthermore, the greatest increase in FA, in addition to MD, AD and RD decrease was observed between birth and 6 years old, in the superior longitudinal fasciculus. The percentage of growth after 6 years old was near zero and 90% of the maximum FA and MD values were reached around 16 and 9 years old, respectively (Uda et al. 2015).

Finally, regarding gender differences, we observed some variations in the maturation timings of the frontal tracts, between females and males. Specifically, lower RD values were observed in the females' inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus (range: 6–17, Asato et al. 2010; Eluvathingal et al. 2007) when compared to males. An exception was observed in the superior longitudinal fasciculus. The frontal portion showed ongoing maturation until early adulthood in the female group; while in males just the parietal portion was fully matured by adolescence (range: 13–17). In the males' group, all the other tracts remained maturing throughout young adulthood (Asato et al. 2010). Additionally, higher FA values were found in the males' superior longitudinal fasciculus and uncinate fasciculus, compared to females; and increased MD was found in the females' superior fronto-occipital fasciculus in comparison to its males' counterparts (range: 5–32, Lebel and Beaulieu 2011).

Despite, other studies found no gender differences in the developmental trajectory of frontal white matter and its association tracts (Bartzokis et al. 2012; Bava et al. 2010; Giorgio et al. 2008; Krogsrud et al. 2016; Kumar et al. 2012; Muftuler et al. 2012; Tamnes et al. 2010; Uda et al. 2015).

Discussion

The purpose of this review was to systematize the current knowledge on the developmental pathway of the frontal cortex in terms of its microstructural connectivity, as shown by DTI metrics. Overall, the findings suggest an extended developmental course of frontal white matter and its main association tracts (superior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior fronto-occipital fasciculus and uncinate fasciculus), as shown by variations in white matter-related indexes (FA, MD, RD and AD). Furthermore, the majority of the studies suggest linear age-related changes observed in FA MD, RD and AD, since birth until adulthood. Despite, some periods of steadiness may also occur during development.

The results of this systematic review documented that frontal white matter maturation continues far beyond the 3rd decade of life, which is consistent with other MRI derived measures, as the reduction of cortical thickness and increasing white matter volume observed throughout adolescence and early adulthood (Tamnes et al. 2010). Specifically, a tendency to increase anisotropy (FA) and decrease diffusivity (MD and RD) as a function of age was observed in the frontal white matter and association tracts. In accordance, the lowest FA values and the highest MD and RD values were observed in infants and children; contrastingly, the highest FA and lowest MD and RD were found in young adults. Furthermore, in comparison to all other brain areas, the lowest FA and highest MD were found in the neonatal frontal lobes (Schneider et al. 2004); whereas the highest FA and lowest MD were observed in the adolescents (> 144 months) and adult frontal regions, possibly reflecting the protracted myelination of the frontal lobes (Schneider et al. 2004). The process of myelination, axonal density and organization and coherence of fibers' orientation within the frontal white matter seem to last until the thirties, as shown by these studies, documenting a linear increase of FA and decrease in MD and RD, but not so consistently AD until this age range. As mentioned earlier, higher values of anisotropy (e.g., FA) are commonly associated with axonal organization, bundles density, coherence of fibers' orientation (Beaulieu 2002; Ding et al. 2013; Scholz et al. 2009), while lower values of diffusivity seem to be related with intact healthy axons (MD and AD; Beaulieu 2002; Preziosa et al. 2017; Sun et al. 2008) and myelin growth (as measured through RD; Alexander et al. 2007; Song et al. 2003; Sun et al. 2006).

Overall, these studies converge in showing that these DTI metrics are sensitive to different aspects of white matter maturation. It is important to note that although greater axonal organization and coherence are events commonly associated to anisotropic diffusion, it is difficult to attribute particular microstructural features to changes in the frontal white matter FA, as it is not possible to know whether FA variation

occurs due to the improved coherence of the fiber tracts, or if it solely results from the myelination process. Still, healthy cellular membranes are supposed to be the major basis of the anisotropic water diffusion in white matter fibers, and myelination is thought to modulate the degree of anisotropic diffusion, even though the currently available methods do not allow dissociating these two microstructural features (Beaulieu 2002). For RD, the available literature suggests that decreased values reflect higher myelination, as myelin sheaths seem to modulate anisotropic diffusion by creating barriers to the displacement of water molecules (Beaulieu 2002) with disruptions of the myelin sheaths being related to increasing RD (Song et al. 2002). Finally, the understanding of the AD measure is more controversial in the literature. While lower AD values are commonly associated with injured axons (Beaulieu 2002; Sun et al. 2008), they may also be related with regulation of axon branching across development (Gallo 2011; Gibson and Ma 2011), increasing number of white matter tracts or increasing axonal caliber across development and consequent inter-axonal space decrease (Beaulieu 2002; Hagmann et al. 2006; Pierpaoli et al. 1996).

Globally, the studies also suggest that the rate of change in anisotropic and diffusion measures appears to be lower in the interval period between 6 and 11 years old (Muftuler et al. 2012; Qiu et al. 2008; Uda et al. 2015). This deceleration with age (between 6 and 11 years) suggests that this developmental period might rather represent a steady period in frontal white matter development, compared to the first years of life (until 4 years old), (Krogsrud et al. 2016) and adolescence. A possible explanation for white matter growth to slowdown in this age interval may be associated with the observed GM increase (Giedd et al. 1999). In fact, a relation between these two events might eventually exist since GM growth seems to peak around age 12 (followed by a decline), yet the cerebral volume appears to remain quite unchangeable after age 6, as shown by MRI studies (Giedd et al. 1999; Giedd 2004; Gogtay et al. 2004; Lenroot and Giedd 2006). In addition, frontal cortical thickness was found to be negatively correlated with the white matter volume and FA values, and positively associated with MD, AD and RD values (Tamnes et al. 2010). Moreover, distinct timings of maturation were observed in the main frontal association tracts. Specifically, some of the tracts were fully matured between adolescence and early adulthood, either in terms of axonal organization (increased FA and decreased MD and AD) or myelin growth (decreased RD), as the inferior fronto-occipital fasciculus (Asato et al. 2010; Bava et al. 2010; Eluvathingal et al. 2007; Lebel and Beaulieu 2011), the superior fronto-occipital fasciculus (Simmonds et al. 2014), and the superior longitudinal fasciculus (Asato et al. 2010; Bava et al. 2010; Lebel et al. 2008); whereas the uncinate fasciculus continued to mature until the thirties (Lebel

et al. 2008; Simmonds et al. 2014). These studies suggested that the myelination of the frontal association tracts (i.e., the fronto-occipital, fronto-parietal and fronto-temporal connections) is practically completed by the end of adolescence (Asato et al. 2010; Lebel and Beaulieu 2011; Simmonds et al. 2014); despite the axons' organization continues throughout adulthood (Lebel and Beaulieu 2011; Lebel et al. 2008). This suggests that myelination is likely to be an ongoing process, which occurs since neonatal ages until late adolescence/early adulthood, while fibers' organization and refinement of axonal connectivity might occur at later ages, since this might be a more complex and demanding process, highly dependent on the individual' interplay with the environment.

The current systematic review offers a characterization of the developmental pathway of frontal white matter, as shown by DTI measures, since neonatal ages until early adulthood. Significant alterations of the DTI indexes measured in the frontal white matter of healthy individuals were observed along the brain development, in parallel with alterations in the fibers' pathways and underlying connectivity. This microstructural remodeling suggests that the frontal regions are in constant reorganization and refinement in response to continuous adaptation to environmental stimulation. Moreover, since the diffusion parameters are sensitive to age-dependent fluctuations, the observed DTI metrics changes across the lifecycle suggest that specific, and possibly non-linear, periods of white matter development exist and that changes in frontal white matter microstructure may be qualitatively distinctive in different developmental periods. As highlighted before, the frontal white matter maturation follows a hierarchical trajectory as changes appear to be more pronounced in infancy, between birth and 6 years old, which is followed by a plateau during childhood-early adolescence (range: 6–10), returning to rise between adolescence and early adulthood, that occur in parallel with improvements in cognitive abilities (Gogtay et al. 2004), and in response to the emergent environmental exigencies at each developmental momentum. For example, brain development between adolescence and early adulthood is associated with increasingly new, complex and highly demanding experiences, such as advanced education, employment, new social relations, new familiar responsibilities, that will ultimately influence and be influenced by brain structural and functional architecture, such is the case of higher level executive functions. Furthermore, associations between DTI metrics of the frontal regions and performance in executive functions-related tasks were previously reported, showing an association between performance and anisotropy values and/or diffusivity measures (Madsen et al. 2010; Nagy et al. 2004; Urger et al. 2015). Specifically, higher FA and lower RD in inferior frontal gyrus of young adolescents were associated to better scores in response inhibition, as measured by

the Stop Signal Task (Madsen et al. 2010). Working memory capacity was also positively correlated with FA in the superior and inferior frontal gyri in a group of adolescents (Nagy et al. 2004). Finally, anisotropic values were positively associated with executive set-shifting and attentional tasks, and diffusivity values were negatively correlated with inhibitory control, suggesting a link between maturation processes and enhanced cognitive functions (Urger et al. 2015). These findings suggest that the microstructural maturation of the frontal white matter tracts, in particular during adolescence, is likely to underlie executive functions performance. In addition to great developmental improvements, adolescence is also a vulnerable period for external factors that negatively affect mainly the frontal cortex. Therefore, it is often a period for the onset of psychopathological disorders and emergence of maladaptive behaviors (for a review see López-Caneda et al. 2014 in binge drinking) that might be predicted by disrupted developmental processes or interfere with the optimal process of brain maturation.

To conclude, although water diffusion related measures might reflect brain's microstructural connectivity, some limitations should be considered. In particular, DTI measures are not intrinsic properties of the tissues but instead, assumptions driven by a conglomerate of knowledge derived from several fields (mathematics, physics, engineering, computer science and neurosciences) that might limit the associations between DTI data and biological variables. Building on this, Jones and Cercignani (2010) discussed several limitations of the methodology. These limitations can be encountered in each step of the DTI pipeline; i.e., image acquisition, pre-processing, tensor estimation or extraction of scalar measures. For example, distortions caused by eddy currents and head motion, defining the most suitable model to diffusion tensor estimation, or the best method to extract the quantitative measures; e.g., ROI, histogram, voxel-based analysis or TBSS. Anyhow, what seems to be the most noticeable handicap of all is the reliability degree that one may have, when interpreting the DTI metrics (FA, MD, RD and AD) in the light of cerebral development and its association with biological processes (Jones and Cercignani 2010; Soares et al. 2013). Taking into account all of these factors and the basic assumption that DTI is grounded in the manipulation of proton spins and not a direct measure of axonal connectivity, it seems to be worth reflecting on the DTI metrics and accept the fact that errors might be present in the data, as much as in other imaging methods. However, until now, DTI appears to be the most reliable imaging method to assess white matter structure in vivo (Neil et al. 2002).

Finally, while restricting our review to DTI, reports that used other diffusion imaging methods (e.g., DSI or HARDI) were excluded, which could add further important information about frontal white matter maturation. Future reviews should focus in the remaining diffusion methods.

Conclusion

In this systematic review we highlight the extended course of frontal white matter maturation, evidenced by DTI measures, and documented that brain development is a continuous long-lasting process, driven by specific developmental events (e.g. synaptic refinement, pruning, myelination), designed to sustain the optimal functioning of neuronal networks that support cognition and behavior. Detailed knowledge about the frontal white matter maturation timing is not only important to understand the development of cognitive functions that are dependent on frontal brain regions but it may also be useful in signaling individuals at risk for developmental disorders.

Compliance with ethical standards

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