Rassegna

# Alterations of cerebral white matter structure in psychosis and their clinical correlations: a systematic review of Diffusion Tensor Imaging studies

## *Alterazioni strutturali della sostanza bianca cerebrale nella psicosi e le relative correlazioni cliniche: una rassegna sistematica degli studi di diffusion tensor imaging*

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**SUMMARY.** Schizophrenia is a common, severe and chronically disabling mental illness. Most of MRI studies in schizophrenia suggest the involvement of white matter (WM) pathology in multiple cerebral regions in the neurobiology of this condition. White matter fiber tracts connecting numerous cortical regions have been the focus of a number of studies using a magnetic resonance technique called "Diffusion Tensor Imaging" (DTI). A literature search of published DTI studies was conducted using the major database National Centre for Biotechnology information (NCBI) PubMed (MEDLINE). Our review covers 95 published papers. We summarise the main DTI findings involving the different brain regions in patients affected by or at high-risk for psychosis; we discuss clinical implications of these white matter disruptions and the limitations of current studies, listing the potential confounds and suggesting potential future research directions.

**KEY WORDS:** DTI, psychosis, schizophrenia, white matter.

**RIASSUNTO.** La schizofrenia è una malattia mentale comune, grave e cronicamente invalidante. La maggior parte degli studi di risonanza magnetica in pazienti affetti da schizofrenia suggerisce il coinvolgimento della sostanza bianca di diverse regioni cerebrali nella patogenesi e nella neurobiologia di questa malattia. I fasci di sostanza bianca interposti tra le diverse regioni corticali sono stati oggetto di numerosi studi che utilizzano una tecnica di risonanza magnetica chiamata "Diffusion Tensor Imaging" (DTI). Nel presente studio è stata condotta una revisione della letteratura sugli studi di DTI pubblicati utilizzando il database National Centre for Biotechnology (NCBI) PubMed (Medline). Questa rassegna comprende 95 articoli pubblicati. Sono stati riportati i principali risultati degli studi di DTI in pazienti affetti da psicosi o ad alto rischio per lo sviluppo di psicosi; sono state discusse le implicazioni cliniche delle alterazioni della sostanza bianca e i limiti degli studi in corso elencando i potenziali fattori di confondimento e suggerendo possibili direzioni future per la ricerca.

**PAROLE CHIAVE:** DTI, psicosi, schizofrenia, sostanza bianca.

### INTRODUCTON

Schizophrenia is a complex psychiatric syndrome comprising of psychiatric symptoms, including auditory hallucinations and delusions, cognitive deficits and social dysfunction[1].

The majority of studies on structural brain changes in patients at ultra-high risk for or affected by psychosis have been based on magnetic resonance imaging. Brain structural MRI is based on the differential behaviour of protons of water molecules in gray and white matter when exposed to a variable magnetic field. The contrast between structures varying in the response to magnetic field alterations allows delineating local groupings of neurons and fibers and determining their sizes in absolute and relative terms[2].

Most of MRI studies in schizophrenia suggest the involvement of white matter (WM) pathology in multiple cerebral regions in the neurobiology of this condition. As normal brain functions are served by macrostructural circuits of cortical and subcortical areas, disturbed communication between brain regions may be the core pathology of psychosis. WM consists of the axonal projections to other neurons and functional brain areas and is therefore key to neural communication. Myelination is initiated prenatally and completed for most tracts within the first year birth but continues during childhood, adolescence and adulthood and has a region-specific course where prefrontal regions myelinate the last[3]. Several lines of evidence point to myelin dysfunction, reduced oligodendrocyte number or integrity, or possibly hyperglutamatergic state[4].

Neurodevelopmental theories have suggested demyelination during adolescence and adulthood to occur in psychosis.

Abnormalities in WM structure and integrity have been correlated with psychotic symptoms, negative symptoms and cognitive deficits[5].

WM is difficult to study in detail with conventional MRI because of its high degree of homogeneity, moreover conventional techniques do not allow for the evaluation of its directionality and organization. WM fiber tracts connecting numerous cortical regions have been the focus of a number of studies using a magnetic resonance technique called Diffusion Tensor Imaging (DTI). It has become established in the last two decades as a valuable research tool. DTI assesses a non-invasive and in vivo quantification of the diffusion characteristics of water molecules: within a magnetic field these molecules tend to align into preferential directions according to their ability to diffuse across or along the arrangement of biological structures that surround them. In the brain water may diffuse freely in all directions (isotropic diffusion), or restricted along one particular direction of structured tissue such as WM tracts and fibers (anisotropy diffusion). Fractional anisotropy is a quantitative dimension and can take values between 0 and 1. If the anisotropy is high, then most of the diffusion occurs in the highly ordered directions, indicating a high level of orientation in the structure, therefore, decreased anisotropy may predict compromised white matter integrity[6]. Other measures used to compare different voxels in term of diffusion are mean diffusivity (MD), radial diffusivity (RD) and relative anisotropy (RA)[7]. Additionally different approaches have been applied to study differences in regional brain anisotropy between subjects: some studies have used voxel based approaches (VBA), where data sets have been processed with reference to FA normalized to a standard anatomical and averaged template, before being compared to similarly processed data sets; other studies have used a region of interest (ROI) approach in region of the brain thought to be implicated to psychosis. DTI is becoming increasingly important in the field of schizophrenia research[8].

The aim of this study was to review the knowledge about the abnormalities of WM in patients at ultra-high risk for psychosis (UHR), patients with a first-episode psychosis (FEP) and chronic schizophrenia patients (SZ) compared with controls (HC), making clearer the role of WM integrity alterations in the etiopathogenesis, anatomical bases and clinical or neuro-cognitive correlates of the disorders.

## METHODS

A literature search of published DTI studies was conducted using the major database National Centre for Biotechnology information (NCBI) PubMed (Medline).

The key words used were: "schizophrenia" and " DTI" or "diffusion tensor imaging", "psychosis" and "DTI" or "diffusion tensor imaging". Studies were included if they satisfied the following criteria: the patient population had a diagnosis of psychosis or was considered at ultra-high risk for psychosis, diffusion tensor imaging was an imaging technique used, the article was published in English. Additionally, they were chosen if they were found to be relevant to the focus of this systematic review.

Our review covers 95 papers published between September 2005 and March 2015: 32 papers were excluded.

## RESULTS

In 25 studies the patient population included people considered at ultra-high risk for psychosis. To be considered at high-risk for psychosis patients had to satisfy almost one of these criteria: 1) they had schizotypal personality features; 2) they had sub-threshold psychotic symptoms; 3) they had a first-degree relative with schizophrenia-like disorder; 4) they had brief psychotic moments with spontaneous remission in less than 1 week (Table 1).

We have decided to mention some of the studies excluded because they can provide additional information.

In a study was examined the ability of DTI to differentiate between UHR, FEP and HC subjects: the results suggest that DTI allowed discrimination of UHR from HC subjects[34].

Patients with only cannabis use disorder (CUD) have also been studied with DTI method: they had lower FA than HC in left inferior FOF[27], and altered FA values in left ILF and left inferior FOF compared to HC; greater consumption of cannabis predicted a greater decrease in left ILF FA in CUD[35].

In the study by Mittal et al.[36] youth at high-risk for psychosis presented neurological disfunction and abnormal neurodevelopment misured by the presence of neurological soft signs (NSS) and a decrease of FA in right/left superior CP at 12 months, controls showed a normative increase while there were no group differences at baseline. NSS predicted a longitudinal decrease in cerebellar-thalamic FA and elevations in negative but not positive symptoms 12 months later.

According to Derosse et al.[37] cumulative risk for psychosis (including low QI, low parental socioeconomic status, history of adolescent cannabis use and childhood trauma, high levels of subclinical psychotic-like experiences) was associated with lower FA in left SLF.

In the study by Skranes et al.[38] very low birth weight children had reduced FA values in CI, CE, CC, ILF, SLF; children with low QI had reduced FA in CE, SLF, ILF; fine motor impairment was related to low FA in CI, CE and SLF; mild social deficits correlated with reduced FA in CE and SLF.

Prenatal and neonatal DTI were obtained in the offspring of mothers with schizophrenia or schizoaffective disorder and matched comparison mothers: there were no group differences in white matter diffusion tensor properties[39].

In 41 studies the patient population included people experiencing a first episode of psychosis. (Table 2)

According to Peters et al.[75] FEP with cannabis use before age 17 showed increased directional coherence in the bilateral UF, anterior CI and FL while these abnormalities were absent in FEP without cannabis use before age 17: this is in contrast with most DTI studies which have produced evidence of WM hypoconnectivity.

In 46 studies the patient population included people with chronic schizophrenia (Table 3).

Tang et al.[110] obtained DTI and magnetic resonance spectroscopy from 40 subjects with schizophrenia: N-Acetylaspartate and DTI anisotropy indices were reduced in medial temporal regions.

Patients with temporal lobe epilepsy and interictal psychosis were studied with DTI by Flügel et al.[111]; they showed lower FA values in both frontal and temporal regions and

Table 1. Main findings of DTI studies in people considered at high-risk for psychosis.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Katagiri et al.[9] | 41 | 23.1 | FA reduced in CC | | increase in FA in the same region in the group with improvement in sub-threshold positive symptoms |
| Bloemen et al.[10] | 37 | 19.5 | Lower FA in bilateral medial FL in patients later developing psychosis compared with HC and lower FA values lateral to the right putamen and left superior TL compared to UHR patients who did not develop psychosis | Positive PANSS scores correlated negatively with FA in right superior TL; UHR patients later developing psychosis have positive PANSS scores negatively correlated with FA in left middle TL | |
| Muñoz Maniega et al.[11] | 22 | 30 | Reduced FA in anterior limb of CI | | |
| Camchong et al.[12] | 22 | 48.5 | Reduced FA values in medial FL white matter | | |
| Nakamura et al.[13] | 15 | 37.7 | FA reduced in UF | FA reduced in right UF with clinical symptoms; FA reduced in left UF with cognitive function | |
| Karlsgodt et al.[14] | 36 | 17.0 | FA reduced in SLF | Lower FA in H and ILF predicted functional deterioration | Absence of age-associated increase in FA in H and ILF |
| Peters et al.[15] | 17 | 21.7 | | FA in UF, AF, CC, PC, AC did not differ between patients that developed or not a psychotic disorder | |
| Peters et al.[16] | 10 | 21.6 | No differences in FA from FEP and HC | | |
| Peters et al.[17] | 10 | 21.6 | Reduced FA in right superior FL and left middle FL | | |
| Bertisch et al.[18] | 39 | | | FA in left subgenual AC, left CG, left LG, right PA, PR demonstrated significant heritability | |
| Hazlett et al.[19] | 30 | 41.4 | FA reduced in left TL, RC and PC but not in AC, LC and PFR | Lower FA in C correlated with more severe negative symptoms | |
| Kyriakopoulos et al.[20] | 17<br>17 | 16.6<br>23.7 | Decreased FA in bilateral SLF, bilateral ILF, bilateral inferior FOF, bilateral corticopontine tracts, left CC and bilateral posterior TL in patients with adolescent-onset; | | |

(*continued*)

(*continued*) - Table 1.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| | | | Decreased FA in bilateral ILF, bilateral inferior FOF, brain stem, cerebellum, right SLF, right CC, right UF, right C, right anterior CR, right posterior TL and corticopontine tract in patients with adult-onset | | |
| Carletti et al.[21] | 32 | 23.4 | FA, RD and AD intermediate in UHR between controls and FEP | Progressive reduction in FA in subjects who developed psychosis | |
| Benetti et al.[22] | 46 | 24.3 | Reduction of FA in left long segment in patients without verbal auditory hallucinations | | The sample is composed by both patients UHR and FEP |
| Hoptman et al.[23] | 22 | 20 | Reduced FA in left posterior C, bilateral angular giry, left inferior frontal gyrus; increased FA in left subgenual anterior C and bilateral pontine tegmental WM and right middle/superior frontal gyri | | |
| Smallman et al.[24] | 12 | 21.0 | Increased FA in left UF | Positive correlation between FA in right AF and hallucinatory experience | |
| Domen et al.[25] | 93 | 29.4 | Did not differ from HC | | |
| Boos el al.[26] | 123 | 26.7 | Higher mean FA in left and right AF | | |
| Epstein et al.[27] | 21 | 16.1 | Lower FA in left ILF, CST bilaterally, left inferior FOF | | |
| Derosse et al.[28] | 67 | 36.1 | Lower FA in inferior FOF and greater asymmetry in UF | | |
| Lener et al.[29] | 49 | 36.5 | Lower FA in CC compared with HC | | This abnormality was more widespread in SZ |
| Lagopoulos et al.[30] | 74 | 21.3 | Lower FA in left anterior CR, anterior TL | | |
| Jacobson et al.[31] | 11 | 11-13 | WM decrease in inferior FOF, C, ILF | | |
| Goghari et al.[32] | 24 | 40.2 | Increase in FA in right fimbria of the fornix | No significant association between FA and QI | |
| Hohenberg et al.[33] | 28 | 20.6 | Increased MD in SLF, posterior CR and CC, increased RD in posterior PL | | |

CC=corpus callosum; UF=uncinate fasciculus; SLF=superior longitudinal fasciculus; H=hippocampus; ILF=inferior longitudinal fasciculus; AF=arcuate fasciculus; PC=posterior cingulate; AC=anterior cingulate; CG=cingulate gyrus; LG=lingual gyrus; PA=pericaudate area; PR=perilentiform region; TL=temporal lobe; PFR=prefrontal region; TR=thalamic radiations; RC=right cingulum; LC=left cingulum; C=cingulum; FMJ=forceps major; FMN= forceps minor; CE=external capsule; CR= corona radiate; CST=corticospinal tract; FOF=fronto-occipital fasciculus; PL=parietal lobe; CP=cerebellar peduncles; PO=parietal-occipital; LDL=low-density lipoprotein; CI=internal capsule; PANSS=positive and negative syndrome scale; WCST= Wisconsin card sorting test; GF=frontal gyrus; BPRS=brief psychiatric rating scale; FL=frontal lobe; OL=occipital lobe; T=thalamus; I=insula.

Table 2. Main findings of DTI studies in people experiencing a first episode of psychosis.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Alvarado-Alanis et al.[40] | 35 | 24.6 | Abnormalities in projection fibers, association and commissural fibers (temporolimbic tract), bilateral fornix, superior and inferior CP | | |
| Chan et al.[41] | 39 | 28.8 | Lower FA values in right ILF | FA values correlated with severity of delusions | |
| Karlsgodt et al.[42] | 12 | 20.9 | Lower FA values in SLF | FA values in the left but not right SLF correlated with performance on a verbal task both in FEP and HC | |
| Mendelsohn et al.[43] | 9 | 26 | No FA differences | | |
| Gasparotti et al.[44] | 21 | 28.5 | Lower FA values in the splenium but in the genu of CC | | |
| Melicher et al.[45] | 77 | 31.1 | Decrease in FA in CC, SLF, ILF, inferior FOF, posterior TR | | |
| White et al.[46] | 31 | 25.2 | No differences | | |
| Wang et al.[47] | 68 | 24.1 | Reduced FA in CC, left TL, right PL, left OL | | |
| Tang et al.[48] | 38 | 16.3 | Reduced FA in right anterior C | Negative correlation between mean FA and PANSS positive symptom score | |
| Begrè et al.[49] | 7 | 22.6 | No differences | | |
| Cheung et al.[50] | 34 | 25.4 | Reduced FA in WM in left anterior and right middle CG, left superior and right middle temporal gyrus, left cuneus and right FL | Positive symptoms correlated positively with FA scores in these regions | |
| Moriya et al.[51] | 19 | 29.9 | No differences | | |
| Price et al.[52] | 20 | 24.9 | No differences in FA in CC | | |
| Peters et al.[17] | 8 | 21.2 | Reduced FA in bilateral PL, left superior TL, right TL, I and left FL | | |
| Szesko et al.[53] | 33 | 25.1 | Lower FA in bilateral UF, left SLF, left inferior FOF | Lower FA in bilateral UF correlated with greater severity of negative symptoms, worse verbal/learning memory functioning | |
| Pérez-Iglesias et al.[54] | 62 | 30.8 | Lower FA in bilateral SLF, bilateral ILF, FMJ, CC and anterior and superior TL | | |

(*continued*)

(*continued*) - Table 2.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Bijanki et al.[55] | 31 | 23.1 | | Significant correlation between global FA and negative symptoms (SANS) | This correlation became non-significant with additioning age as a covariate |
| Price et al.[52] | 19 | 23.8 | FA reduced in left UF | No correlations between FA and clinical ratings | |
| Luck et al.[56] | 32 | 23.6 | FA reductions in the fornix | No significant correlation between FA and clinical or socio-demographic data | |
| Kong et al.[57] | 15 | 24.3 | No significantly decreased FA | | |
| Schneiderman et al.[58] | 23 | 16.1 | Decreased FA in TL and SLF | Older age of onset tended to be associated with higher FA in ventral CI and ventral temporo-occipital WM | The study suggest that symptoms associated with the temporal lobe including auditory hallucinations would present before frontal associated symptoms including problem in executive functioning |
| Chen et al.[59] | 20 | 46.9 | Reduction in FA in left PL, right PC | No significant correlations between FA value and PANSS and cognitive test scores, age and antipsychotic medication dosages | Late-onset schizophrenia |
| Friedman et al.[60] | 40 | 26 | Lower FA in ILF | | |
| Peters et al.[61] | 30 | 22.7 | Lower FA in CC, bilateral PL, OL, FL, TL WM | FA correlated with polyunsaturated fatty acid concentration and negative correlated with negative symptoms | |
| Hao et al.[62] | 21 | | Lower FA values in cerebral peduncle, frontal regions, inferior temporal gyrus, medial PL, hippocampal gyrus, I, right anterior C and right CR | | |
| Carletti et al.[21] | 15 | 24.1 | Widespread reduction in FA and increases in diffusivity compared to HC and UHR | | |
| Cheung et al.[63] | 25 | 29 | Lower FA values in left FOF, left ILF, WM adjacent to right precuneus and right substantia nigra, CC, right posterior limb of CI and left cerebral peduncle | | |

(*continued*)

(*continued*) - Table 2.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Epstein et al.[35] | 34 | 16.4 | Lower FA in bilateral CST, bilateral ILF, bilateral inferior FOF compared to HC | | |
| Epstein et al.[27] | 55 | 16.9 | Lower FA than HC in bilateral CST, left ILF, left inferior FOF | | |
| Szesko et al.[64] | 35 | 21.5 | FA reductions within PL and OL WM | Greater overall FA increases in patients with greater increases in LDL | No significant FA increases among patients following treatment |
| Lee et al.[65] | 17 | | Lower FA in genu and body of CC, UF, C, superior and inferior FOF, fornix, CE and CI, increased MD and RD in all WM regions; no difference for AD | FA in right inferior FOF had a positive correlation with negative, positive symptoms and all the items of WCST, FA of right CE showed positive correlation with category completed scores of WCST | |
| Price et al.[66] | 18 | 23.6 | Reduced FA in CC | | |
| Qiu et al.[67] | 32 | 28 | No differences in FA | Left thalamic FA correlated with spatial working memory deficits | |
| Dekker et al.[68] | 26 | 21.1 | Reduced FA in CC in cannabis naïve FEP compared with FEP with early-onset cannabis use and with HC | | |
| Quan et al.[69] | 16 | 21.1 | FA reduced in inferior GF-striatum tract, RD increased in bilateral rostral middle GF-striatum and bilateral inferior GF-striatum tracts | The number of WCST categories completed correlated positively with FA of right rostral middle GF-striatum tract and negatively with RD of right rostral middle GF-striatum tract, right inferior GF-striatum tract; BPRS score had no correlations | |
| Szesko et al.[70] | 10 | 26.9 | Reduced FA in left middle frontal gyrus, left posterior temporal gyrus, left CI | | |
| Kiriakopoulos et al.[71] | 19 | 17.0 | Lower FA in bilateral parietal association and left middle CP, no areas with higher FA | | |
| Marques et al.[72] | 63 | 27.7 | Non responders to treatment at baseline showed lower FA in UF, C, CC | | After 12 weeks increase in FA in responders and non responders positively correlated to antipsychotic exposure |

(*continued*)

(*continued*) - Table 2.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Peters et al.[16] | 10 | 21.2 | No differences | | |
| Lu et al.[73] | 21 | 22 | Greater AD, RD, MD in CC, C, CR, posterior TL, CI, ILF, inferior FOF | | |
| Luck et al.[74] | 44 | 23.3 | FA reduction in bilateral UF and bilateral SLF but not in C | Greater WM changes in these tracts with poor outcome as compared to patients with good outcome | |

CC=corpus callosum; UF=uncinate fasciculus; SLF=superior longitudinal fasciculus; H=hippocampus; ILF=inferior longitudinal fasciculus; AF=arcuate fasciculus; PC=posterior cingulate; AC=anterior cingulate; CG=cingulate gyrus; LG=lingual gyrus; PA=pericaudate area; PR=perilentiform region; TL=temporal lobe; PFR=prefrontal region; TR=thalamic radiations; RC=right cingulum; LC=left cingulum; C=cingulum; FMJ=forceps major; FMN= forceps minor; CE=external capsule; CR= corona radiate; CST=corticospinal tract; FOF=fronto-occipital fasciculus; PL=parietal lobe; CP=cerebellar peduncles; PO=parietal-occipital; LDL=low-density lipoprotein; CI=internal capsule; PANSS=positive and negative syndrome scale; WCST= Wisconsin card sorting test; GF=frontal gyrus; BPRS=brief psychiatric rating scale; FL=frontal lobe; OL=occipital lobe; T=thalamus; I=insula.

higher MD in bilateral frontal regions, additionally the performance on some neuropsychological tests was related to frontotemporal FA reduction. Mao et al.[112] investigated interictal personality changes and white matter abnormalities in epilepsy patients: long disease duration and impairment of right AF integrity were independent risk factor of psychoticism.

Cocchi et al.[113] studied the relationship between structural and functional deficits in schizophrenia patients: they showed decreased functional connectivity and impaired white matter integrity in a distributed network encompassing frontal, temporal, thalamic and striatal regions; in controls strong interregional coupling in neural activity was associated with well-myelinated white matter pathways.

Compared with Parkinson's disease patients without psychosis, those with psychosis had significantly lower FA in left frontal lobe, bilateral occipital lobe, left cingulated gyrus and left hippocampus[114].

For an overview of the results see table 4.

## DISCUSSION

The findings can be grouped into WM pathology affecting cortical regions, subcortical regions, inter-hemispheric fibers, association fibers and limbic system fibers. Corpus callosum consists of a commissural tract comprising the largest bundle of fibers connecting the two brain hemispheres.

Association fibers are: SLF which connects the frontal lobe with occipital and temporal areas, ILF, UF which are anterior temporo-frontal fiber tracts connecting orbito-frontal with anterior and medial temporal lobes, FOF which extends backward from the frontal lobe and spreading into the temporal and occipital lobes, AF is a fiber tract that stems from the caudal part of the superior temporal gyrus and extends to the lateral prefrontal cortex, the superior and the middle frontal regions. Limbic system fibers are the cyngulum fibers that project both posteriorly from the cingulate gyrus to the entorhinal cortex, temporal lobe, and anteriorly to the premotor, prefrontal regions and striatum. The fornix connects the hippocampus to the mamillary bodies, nucleus accumbens, medial prefrontal cortex, and septal regions, thus this fiber serves as the main output and input pathway for hippocampus. Thalamic radiations are projection fibers that provides a functional loop between the cerebral cortex and the thalamus; they converged into the internal capsule, located between the putamen and the thalamus-caudate nucleus regions[5].

Changes in WM integrity were found in chronic psychosis, first-episode psychosis and patients at ultra-high risk for psychosis, they may play a role in the primary pathophysiology, as opposed to being a result of secondary disease processes. These changes have been correlated with specific cognitive deficits as well as clinical symptoms, suggesting that biological changes may underlie these clinical factors in patients.

Previous DTI studies assessing the impact of WM disruptions on the disease process have had mixed results. Our study adds to a growing body of literature emphasizing the need for treatments targeting white matter function and structure in psychosis patients.

The main findings in patients at ultra-high risk for psychosis were a decreased FA in inferior FOF, temporal lobe WM, frontal lobe WM. They seem to have predictive value of onset of psychosis in high-risk individuals. Other studies in ultra-high risk patients showed lower FA in anterior CR, corticospinal tracts, SLF, ILF, UF, CC and C. In addition, increase of FA values was seen in anterior C, left UF, AF, frontal lobe WM, right fornix and brain stem. The prediction of psychosis is a major topic in research and olds the hope for early intervention and prevention of full development of the illness, improving outcome and preserving WM integrity.

Decreases of FA in different tracts in patients at first-episode psychosis support notion of early disconnectivity between brain regions: the most burned were CC, UF, ILF, SLF, inferior FOF, temporal lobe WM, parietal lobe WM and left frontal lobe WM. White matter abnormalities were also observed in C, occipital lobe, CI, corticospinal tracts, cerebral

Table 3. Main findings of DTI studies in people affected by chronic schizophrenia.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Palaniyappan et al.[76] | 17 | 33.0 | Reduction in FA in LG | Predicted impaired processing speed | |
| Munõz Maniega et al.[11] | 31 | 37 | Lower FA in bilateral UF, left AF, bilateral anterior limb of CI | | |
| Nazeri et al.[77] | 44 | 36.0 | Reduced FA in left posterior PO cluster and left FL | FA in FL predicted attention, processing speed, working memory in HC but not in SZ | |
| White et al.[46] | 83 | 36.4 | Reduced FA in the whole brain | | |
| Hoptman et al.[23] | 23 | 36.8 | Reduced FA in left superior and middle temporal giry, left ILF, left C, left inferior frontal gyrus, right perilentiform regions; higher FA in left LG, I and right deep frontal WM | | |
| Schneiderman et al.[58] | 35 | 43.1 | Reduced FA in C, CC, right anterior TL, FOF | | |
| Orfei et al.[78] | 45 | 38.8 | No significant results | No significant relationship for self-certainty and global cognitive insight | |
| Roalf et al.[79] | 25 | 36.7 | FA reduced in bilateral FL, TL, OL WM and CC | | higher FA in LC and left FOF only in HC but not in SZ |
| Lener et al.[29] | 22 | 33.2 | Lower FA in C, CC, ILF, anterior limb of CI | Greater overall symptom severity correlated with lower FA in CC, left ILF and left anterior limb of CI | The abnormality in CC was more widespread than UHR |
| Hatton et al.[80] | 42 | 22.7 | Reduced FA and AD in left ILF, SLF and FMJ | The abnormalities in left ILF and FMJ correlated with worse symptom severity and worse levels of depression; those in SLF correlated with impaired neurocognitive performance | The patients were at early stage of disease |
| Cullen et al.[81] | 43 | 37.0 | Lower FA in smoking SZ in total cortical, FL, total brain, OL | Among smoking and non smoking SZ FA was correlated with QI | Smoking SZ differed from non smoking SZ in FL, but these differences were no longer significant after QI correction |
| Marenco et al.[82] | 15 | 30.6 | Reduced total connectivity of the thalamus to PFR cortex | The total thalamo-cortical connectivity to PFR predicted working memory task performance | |

(*continued*)

(*continued*) - Table 3.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Yan et al.[83] | 33 | 23.1 | Decreased FA in right AC | Correlated with stroop performance and symptom severity | |
| Camchong et al.[84] | 29 | 41.3 | Connectivity alteration in medial frontal e AC | Frontal connectivity is positively associated with symptoms and general cognitive ability measures | |
| Lagopoulos et al.[30] | 69 | 22.4 | Lower FA in left anterior CR, anterior TL | | |
| Weijer et al.[85] | 44 | 36.9 | Decreased FA in CST, UF and C | Negative correlation between FA and age | The sample is composed by SZ with chronic severe hallucinations |
| Abdul-Rahman et al.[86] | 33 | 39.4 | Reduction in FA in bilateral fornix and left AC, increase in RD in left AC and bilateral fornix, increase in AD in anterior left middle C | Decreased FA in left fornix and increased AD in RC correlated with greater severity of psychotic symptoms | |
| Ardekani et al.[87] | 50 | 30.3 | FA and MD values can be used to distinguish between SZ and HC | | |
| Choi et al.[88] | 25 | 44.6 | Decrease in mean FA in anterior commissure | Anterior commissure integrity correlated negatively with age and decision making and correlated positively with total positive symptom score | |
| Friedman et al.[60] | 40 | | Lower FA in most regions compared to HC | | |
| Antonius et al.[89] | 36 | 37.4 | Right superior GF, left middle GF, bilateral parahippocampal gyrus, right T, left I, left fusiform gyrus, bilateral PC and left lentiform nucleus, left AC, RC, left LG, bilateral claustrum | These abnormalities correlated with symptom unawareness; deficits of WM in right LG, left middle temporal gyrus and right precuneus related to misattribution of symptoms | No HC |
| Boos et al.[26] | 126 | 26.6 | No difference in mean FA between SZ and HC; excessive decline in mean FA in genu, left UF, left inferior FOF, left ILF with increasing age | Negative correlation between FA in bilateral AF and symptom severity | SZ were young adult |
| Filippi et al.[90] | 43 | 29.3 | Decreased MD and increased FA in right anterior and posterior limb of CI, bilateral interhemispheric and corto-cortical connections, bilateral cerebellum and brain stem | These abnormalities related to a longer duration of the untreated psychosis and severity of positive symptoms | |

(*continued*)

(*continued*) - Table 3.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Domen et al.[25] | 85 | 28.3 | Lower mean FA in CC, FMJ, FMN, bilateral CE, bilateral CR, bilateral posterior TR | | |
| Sungranyes et al.[91] | 25 | 17.1 | Reduced FA in splenium and PC | | |
| Wagner et al.[92] | 38 | 35.8 | Lower FA in right anterior limb of CI, right T, right CC | FA in right anterior limb of CI correlated with cognitive performance | |
| Balevich et al.[93] | 34 adults<br>17 adolescents | 43.7<br>15.9 | Adults most reduction in posterior region<br>Adolescent most reduction in anterior region | Negative correlation between negative symptoms and FA in right posterior lateral body in adults and left medial anterior body in adolescents | |
| Bijanki et al.[55] | 59 | 37.7 | | Global negative symptoms correlated with global FA , upon addition of age as a covariate the relationship became non-significant | |
| Goghari et al.[32] | 25 | 41.3 | | No significant relationship between FA and QI, symptoms or global functioning | |
| Garver et al.[94] | 13 | 33.7 | Increase of diffusivity in SZ considered drug-responders | This pathological increase in diffusivity was reduced following treatment-associated reduction of psychotic symptoms | Diffusivity of SZ considered poor responders did not differ from HC at baseline and following treatment |
| Rosenberger et al.[95] | 27 | 39.1 | Decline in FA with age in SZ in C and UF but not in inferior FOF | | |
| Skelly et al.[96] | 25 | 34.2 | FA reduction in multiple bilateral posterior limb of CI and bilateral CR (but stronger on the left hemisphere), in C (bilateral medial TL and right FL) , left ILF, left anterior TR, FMN and right inferior FOF | Inverse relationship of FA in left UF and left SLF with positive symptom score; positive correlation between negative symptoms and FA in right I | |
| Nestor et al.[97] | 18 | 39.1 | | FA in left C correlated with orienting of attention | |
| Liu et al.[98] | 10 | 25.6 | Lower FA in left superior CP | | |
| Caprihan et al.[99] | 65 | 33.6 | Abnormalities in TR, CST, FMJ, FMN, SLF, superior FOF | | |

(*continued*)

(*continued*) - Table 3.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Cui et al.[100] | 25 | 25.8 | Reduced FA in left posterior CR | Negative correlation between FA in left frontoparietal lobe and positive symptom score; no correlation with duration of illness | |
| Kong et al.[57] | 15 | 24.3 | Decreased FA in CC in SZ | | |
| Levitt et al.[101] | 16 | 39.4 | No differences | FA in anterior limb of CI correlated positively with performance on measures of spatial and verbal declarative/episodic memory | |
| Knochel et al.[102] | 21 | 38.3 | Changes in MD in bilateral C and right UF; lower FA and higher MD in fornix in comparison with HC; lower FA in bilateral UF; higher MD in bilateral UF in HC | No correlation with clinical parameters or with years of medication | |
| Whitford et al.[103] | 24 | 39.6 | Subnormal levels of FA in fibers connecting the rostral with the caudal anterior CG and the isthmus of C with parahippocampal cortex | FA in fibers connecting the rostral with the caudal anterior CG correlated with positive symptoms, FA in fibers connecting the isthmus of C with parahippocampal cortex correlated with negative symptoms | |
| McCarthy-Jones et al.[104] | 113 | 39.1 | Reduced FA and increased RD in left AF in patients with Auditory Verbal Hallucinations (AVH) compared to HC and SZ without AVH | | |
| Sasamoto et al.[105] | 35 | 36.6 | Lower mean of FA in CC, bilateral UF, CST, left SLF and superior FOF in SZ | Mean FA showed positive correlation with mean cortical thickness | |
| Kawashima et al.[106] | 15 | 24.5 | Reduced FA in bilateral UF but not in C | | Early stage of illness |
| Hatton et al.[107] | 42 | 22.7 | Reduced FA in short association fibres connecting the superior and the middle temporal gyri | | Adolescent-onset psychosis subjects showed FA reductions in short association fibres connecting superior temporal gyrus and Heschl's gyrus when compared to adult-onset subjects |

(*continued*)

(*continued*) - Table 3.

| Authors | Sample | Mean age (years) | Abnormalities | Correlations | Comments |
|---|---|---|---|---|---|
| Zou et al.[108] | 21 | | Reduced FA in bilateral anterior limb of CI | | |
| Giezendanner et al.[109] | 34 | 33.6 | SZ born in summer had lower FA in CC, bilateral inferior FOF, bilateral UF, right anterior CR, left posterior C, bilateral posterior CR, left posterior TR, bilateral CST, bilateral SLF, FMJ | Later age of onset was found in SZ born in winter months | |

CC=corpus callosum; UF=uncinate fasciculus; SLF=superior longitudinal fasciculus; H=hippocampus; ILF=inferior longitudinal fasciculus; AF=arcuate fasciculus; PC=posterior cingulate; AC=anterior cingulate; CG=cingulate gyrus; LG=lingual gyrus; PA=pericaudate area; PR=perilentiform region; TL=temporal lobe; PFR=prefrontal region; TR=thalamic radiations; RC=right cingulum; LC=left cingulum; C=cingulum; FMJ=forceps major; FMN= forceps minor; CE=external capsule; CR= corona radiate; CST=corticospinal tract; FOF=fronto-occipital fasciculus; PL=parietal lobe; CP=cerebellar peduncles; PO=parietal-occipital; LDL=low-density lipoprotein; CI=internal capsule; PANSS=positive and negative syndrome scale; WCST= Wisconsin card sorting test; GF=frontal gyrus; BPRS=brief psychiatric rating scale; FL=frontal lobe; OL=occipital lobe; T=thalamus; I=insula.

peduncles and fornix. None of the studies included showed increased FA in patients with first-episode psychosis.

DTI abnormalities in first-episode patients are less robust than in chronic patients, suggesting that progression to more extensive abnormalities occurs after illness onset; there are also indications for accelerated aging effects in psychosis.

FA reductions were found in patients with chronic psychosis in CC, C, UF, left ILF, inferior FOF, SLF, FMN, FMJ, CR, corticospinal tracts, anterior CI, TR, temporal lobe WM, occipital lobe WM and frontal lobe WM. Changes in WM integrity have been reported also in left AF, superior FOF, fornix and hippocampus.

White matter tracts that were reported to have increased FA in almost one study include brain stem, right frontal lobe WM, left occipital lobe WM, insula, CI, cerebellum, inter-hemispheric and cortico-cortical tracts.

Of the included studies, 13 did not report group differences in anisotropy measures between patients and controls (3 in ultra-high risk patients, 8 in first-episode psychosis, 2 in chronic psychosis).

38 of the included studies (7 in UHR, 12 in FEP, 19 in SZ) found significant correlations between clinical or cognitive variables and FA values in some WM tracts. 3 studies showed a negative correlation between the severity of positive symptoms and FA values in some WM tracts like temporal lobe WM, right anterior C, right frontal lobe WM, cingulated gyrus WM, left fornix, right anterior and posterior limb of CI, left UF, left SLF, fibers connecting the rostral with the caudal anterior CG, bilateral inter-hemispheric and cortico-cortical connections, cerebellum and brain stem. Regarding to hallucinatory experience a positive correlation was found with FA values in right AF, while severity of delusions was associated with FA values in right ILF.

In 3 studies negative symptoms were correlated negatively with FA values in some WM tracts including C, bilateral UF, CC, TL, OL, PL, FL and fibers connecting C with parahippocampal cortex; in one paper a positive correlation was found between negative symptoms and WM integrity in right I.

FA values showed a relation with clinical symptoms in right UF, CC, left ILF, left anterior limb of CI, FMJ, right AC, frontal connectivity and bilateral AF.

Cognitive function was found to be related with WM deficits in left and right UF, right CE, SLF, right AC, frontal connectivity, right anterior limb of CI (this one was found to be proportional to performance on measures of spatial and verbal declarative/episodic memory). Left thalamic FA values correlated with spatial working memory deficits. Fractional anisotropy in right rostral middle GF-striatum tract correlated positively with the number of WCST categories completed; FA reduction in LG predicted impaired processing speed while FA in left C correlated with orienting of attention. According to Marenco et al.[82] the total thalamo-cortical connectivity to PFR predicted working memory task performance.

On the contrary, according to Lee et al.[65] FA in right inferior FOF had a positive relation with negative, positive symptoms and all the items of WCST; similarly, according to Choi et al.[88] anterior commissure integrity correlated negatively with decision making and positively with total positive symptoms score. In UHR patients increase in FA in CC was found to be correlated with improvement in subthreshold positive symptoms while, in other samples, patients later developing psychosis had lower FA values in several tracts. In less numerous papers FA values did not differ between UHR patients that developed or not a psychotic disorder.

Functional deterioration in UHR was predicted by lower FA values in H and ILF, Goghari et al.[32] didn't find significant relationship between FA and global functioning.

On the other side, no correlation with clinical/cognitive measures were found in 8 of the studies included (2 in UHR, 3 in FEP, 3 in SZ).

Table 4. Summary of DTI findings.

| White matter tract or area | UHR | | FEP | | SZ | |
|---|---|---|---|---|---|---|
| | Decrease FA | Increase FA | Decrease FA | Increase FA | Decrease FA | Increase FA |
| Corpus callosum | 2 | | 9 | | 9 | |
| Left | 2 | | | | | |
| Right | 1 | | | | | |
| Cingulum | 2 | | 2 | | 9 | |
| Anterior | | 1 | 3 | | 2 | |
| Posterior | 1 | | 1 | | 2 | |
| Uncinate fasciculus | 2 | | 4 | | 8 | |
| Right | | | | | | |
| Left | | 1 | 1 | | | |
| Arcuate fasciculus | | 1 | | | | |
| Right | | | | | | |
| Left | | | | | 2 | |
| Inferior longitudinal fasciculus | 2 | | | | 1 | |
| | | | 4 | | | |
| Right | | | 1 | | | |
| Left | 1 | | 2 | | 4 | |
| Superior longitudinal fasciculus | 2 | | 5 | | 3 | |
| Right | | | | | | |
| Left | | | | | | |
| Fronto-occipital fasciculus | | | 2 | | 1 | |
| Superior | | | 1 | | 2 | |
| Inferior | 4 | | 5 | | 3 | |
| Temporal lobe | 3 | | 6 | | 5 | |
| Left | 1 | | 2 | | | |
| Right | | | | | 1 | |
| Parietal lobe | 1 | | 5 | | | |
| Right | | | 1 | | | |
| Left | | | 1 | | | |
| Occipital lobe | | | 2 | | 3 | |
| Left | | | 1 | | | 1 |
| Right | | | | | | |
| Frontal lobe | 4 | 1 | 1 | | 5 | |
| Left | | | 3 | | 2 | |
| Right | | | 2 | | | 1 |
| Hippocampus | | | 1 | | 2 | |
| Thalamic radiations | | | | | 3 | |
| Posterior | | | 1 | | 2 | |
| Anterior | | | | | 1 | |
| Internal capsule | | | 2 | | | 1 |
| Anterior | 1 | | | | 5 | |
| Posterior | | | 1 | | 1 | |
| External capsule | | | 1 | | 1 | |
| Anterior | | | | | | |
| Posterior | | | | | | |
| Corona Radiata | | | | | 3 | |
| Anterior | 2 | | 1 | | 2 | |
| Posterior | | | | | 2 | |

(*continued*)

(*continued*) - Table 4.

| White matter tract or area | UHR | | FEP | | SZ | |
|---|---|---|---|---|---|---|
| | Decrease FA | Increase FA | Decrease FA | Increase FA | Decrease FA | Increase FA |
| Corticospinal tracts | 2 | | 2 | | 4 | |
| Cerebellar peduncules | | | 1 | | 1 | |
| Cerebral peduncles | | | 2 | | | |
| Insula | | | 1 | | 1 | 1 |
| Cerebellum | 1 | | | | | 1 |
| FMN | | | | | 3 | |
| FMJ | | | 1 | | 4 | |
| Fornix<br>Right<br>Left | | 1 | 2 | | 2 | |
| Anterior commissure | | | | | 1 | |
| Inter-hemispheric and cortico-cortical tracts | | | | | | 1 |
| Brain stem | 1 | 1 | | | | |

Antonius et al.[89] studied the relation between symptoms unawareness and WM abnormalities, suggesting that misattribution of symptoms may be implied by loss of WM integrity in right LG, TL and right precuneus.

The impact of medications on WM integrity is far from well understood. The vast majority of patients participating in DTI studies to date have been on antipsychotic medication treatment. Although medication dose or cumulative exposure do not correlate with FA in most studies; some studies reported positive findings: according to Marques et al.[72] patients non-responders to treatment at baseline showed lower FA in UF, C, CC; additionally, in the same sample after 12 weeks increase in FA positively correlated to antipsychotic exposure.

Interestingly, in 2 studies FA values have been associated with metabolic measures like greater levels of LDL or polyunsaturated fatty acid concentration.

Several studies have shown age-related reduction in FA in schizophrenia, whereas other studies did not replicate this relationship. While some studies that examined correlations with age failed to identify a significant effect, 5 of the included papers showed significant negative correlation between FA and age. Additionally, SZ adults showed most FA reduction in SNC posterior region, while SZ adolescents had most FA reduction in SNC anterior region. Karlsgodt et al.[14] found the absence of age-associated increase in FA in H and ILF in UHR patients.

Some studies pointed out the effect of some socio-demographic variables like gender, duration of untreated psychosis, duration of illness and age of onset on WM changes. Older age of onset tended to be associated with higher FA in ventral CI and ventral temporo-occipital WM, while adolescent-onset psychosis subjects showed WM anomalies in short association fibers connecting superior temporal gyrus and Heschl's gyrus; suggesting that symptoms associated with TL WM anomalies including auditory hallucinations would present before FL WM symptoms including problem in executive functioning. Later age of onset was found in SZ born in winter months, SZ born in summed had lower FA in CC, bilateral inferior FOF, bilateral UF, right anterior and bilateral posterior CR, left posterior C, left posterior TR, bilateral SLF, bilateral CST and FMJ. Filippi et al.[90] found abnormalities in right anterior and posterior limb of CI, bilateral inter-hemispheric and cortico-cortical connections, cerebellum and brain stem to be related with a longer duration of untreated psychosis. Cui et al.[100] showed no correlation of WM anomalies with duration of illness. No significant associations were found between FA and QI in 2 papers, but in another one SZ patients had FA values proportional to QI and differences between smoking and non-smoking SZ were no longer significant after QI correction.

Focusing particularly on patients outcome, increase in FA values in affected tracts was predictive of improvement in symptoms and good outcome, while greater WM changes in some of these tracts, like bilateral UF and bilateral SLF, were associated with poor outcome.

There is a need to better understand the relationship between neural changes with clinical manifestations, cognitive and social functioning and outcome. Understanding the progression of these changes over the span of the illness is important whilst taking into account the possible confounding effects of age, age of onset, duration of illness, sex, and treatment. This will potentially allow better staging of illness, identification of biomarkers for monitoring course of the illness as well as response to treatment.

## CONCLUSIONS

In conclusion, despite heterogeneity of DTI findings in psychosis, there is mounting evidence of disruptions of white matter integrity in cortical-subcortical brain regions, as well as associative and commissural tracts, highlighting neural changes in patients affected by or at high-risk for psychosis.

Future studies need to validate these findings in larger samples of subjects and in different populations as well as chart the progress of these cerebral WM changes over time so as to better appreciate the trajectory with illness course, treatment and chronicity.

Particularly, it can be useful combining DTI studies to functional RMN methods in order to investigate mediating factors that will enhance our knowledge about pathophysiology of psychosis.

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