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Abnormal Developmental Trajectories of White Matter in Autism - The Contribution of MRI

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1. Introduction

Autism spectrum disorder (ASD) is a disorder of neuronal connectivity. It has been suggested that disturbed, abnormal and disorganized inter- and intra–cortical connections are one of the core issues in autism[1], resulting in poorly synchronized and weakly responsive networks, which in turn lead to abnormal cognitive and neurological functioning. Evidence accumulated in recent years has led to a shift in the conceptualization of autism, from a localized neurological abnormality to a disorder of distributed networks throughout the brain.

What is connectivity? Two fundamental principles of brain organization have been proposed: functional specialization and functional integration (Friston, 1994, 2002), with the understanding that these two principles are complementary. Functional specialization is usually inferred by the presence of activation foci while functional integration is regarded as a process mediated by connectivity, which reflects the patterns of interaction between neuronal populations, either during the performance of specific tasks or during resting state (Friston, 1994, 2002, 2009a, 2009b; Honey et al., 2009).

Functional integration relies on functional and structural connectivity, while taking into account that these two are not necessarily co-referential (Honey et al., 2009), and that the functional-structural relationship is not straightforward (Damoiseaux & Greicius, 2009). Functional connectivity, as studied by functional magnetic resonance imaging (fMRI), refers to the temporal synchronization of the blood oxygenation level dependent (BOLD) signal of two or more brain areas. Structural connectivity on the other hand, as measured by diffusion tensor imaging (DTI), refers to the physical properties of structural connections - the way in which different brain regions are connected, at the macro level (bundles of axonal tracts) (Mori & van Zijl, 2002).

1.1 The under-connectivity theory in autism

Postmortem and imaging studies support the central role of disordered brain connectivity in autism, and emphasize the importance of studying structural and functional connectivity within the brain. Just et al (Just et al., 2004) formulated the "under-connectivity" theory of

[1] In this chapter, the term autism will be equivalent to the acronym ASD, referring collectively to the broader spectrum. When referring solely to the autistic disorder (subgroup), this will be specified.

autism, arguing that ''autism is a cognitive and neurobiological disorder marked and caused by underfunctioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels''. This theory has gained much attention in a large number of studies investigating functional and structural connectivity (for more information see: Belger et al., 2011; Geschwind & Levitt, 2007; Müller, 2007; Wass, 2010).

While there is growing consensus that autism is associated with atypical brain connectivity, there is less agreement regarding the under-connectivity theory, and the location of these abnormal networks. Studies using various methodologies, such as EEG, MEG, fMRI and DTI have reported evidence of under-connectivity in autism (Brock et al., 2002; Castelli, 2002; Just et al., 2004), while others treat the problem as one of over-connectivity (Belmonte & Yurgelun-Todd, 2003; Courchesne & Pierce, 2005; Hutsler & Zhang, 2010).

Several explanations have been proposed to reconcile these two ideas. Belmonte (Belmonte et al., 2004) suggested that ''high local connectivity may develop in tandem with low long-range connectivity''. This was further supported by other studies reporting a deficiency in the quality of long-range cortico-cortical connections in ASD (Hughes, 2007; Jou et al., 2011) and an increase in short-range connections, as well as connections between subcortical areas and the cortex (Mizuno et al., 2006). In addition, specific methodological characteristics including the choice of tasks were found to affect the results reported in different functional connectivity MRI studies (Müller et al., 2011).

In summary, it is likely that alteration of structural organization underlies functional and behavioral impairment in ASD. As a developmental disorder, we should focus on the trajectories of brain development, in order to better understand the pathology underpinning autism. This will enable better understanding of the nature of this disorder. This chapter will focus on structural connectivity in subjects with autism as detected using MRI with the aim of investigating the integrity and developmental changes of white matter (WM) across the life span. In order to understand abnormal development, a brief review of normal development will first be presented.

2. Normal brain development

The development of the human brain involves extensive structural and neuro-chemical dynamic changes throughout life, with different tissue types, brain structures, and neural circuits exhibiting distinct developmental trajectories. Structural MRI provides information regarding brain development and characterizes age-related changes in brain volume, maturation, cortical thickness and gyrification (Giedd & Judith L. Rapoport, 2010a; Gogtay et al., 2004; Power et al., 2010; Shaw et al., 2008; Vol & Morfologicas, 2000). The focus of this review is WM development therefore the discussion of gray matter (GM) changes will be limited.

2.1 Volumetric changes during brain development

Age-related changes in GM and WM volume have been shown to vary according to sex and brain region. Converging results have been reported by numerous studies, including a large-scale longitudinal study performed at the Child Psychiatry Branch of the National Institute of Mental Health (Giedd et al., 2010; Lenroot & Giedd, 2006). The general pattern for typical brain development in the first 25 years of life is a roughly linear age-dependent increase in WM volume with a steeper increase in males than females. Curves for WM

development did not significantly differ between various lobes (Giedd et al., 1999). At the age of 5, 90% of the adult brain volume had already developed (Giedd et al., 1996), and only a small increase in volume was detected later in life (Giedd et al., 1999). The general increase in WM volume throughout childhood and adolescence may reflect greater connectivity and integration of disparate neural circuitry.

In contrast, GM structures show a general pattern of regionally specific inverted U shaped developmental trajectories, with peak volumes occurring in late childhood or early adolescence (Lenroot & Giedd, 2006). Developmental curves for the different cortical regions significantly differed from each other; those for frontal and parietal lobes were the most similar. The absolute size of the cortical GM was approximately 10% larger in boys, and peaked slightly earlier in girls, although the shape of the curves was not significantly different between boys and girls (Giedd et al., 1999).

Brain development including maturation of functional networks and the specific timing and synchronization of the developmental processes across different brain regions should correlate with the well-known temporal sequences of behavior development. Abnormal development of some brain areas will affect the developmental trajectories of networks and cause a failure to acquire normal behavior.

2.2 Diffusion Weighted Imaging (DWI) & Diffusion Tensor Imaging (DTI)

While conventional MRI methods can provide information about changes in the volume and shape of brain structure, diffusion weighted imaging (DWI) can provide additional information characterizing the microstructure of the tissues (Basser & Jones, 2002; Le Bihan, 2003; Moseley et al., 1990). DWI can detect, indirectly, differences between tissue compartments such as size and geometrical shape. Some compartments have isotropic shape (i.e. the water motion is roughly equivalent in all directions, such as in the CSF) while other compartments have anisotropic shape (i.e. the diffusion is more restricted in one axis, which results in anisotropic diffusion, such as in the WM). Diffusion tensor imaging (DTI) can detect information regarding the size and shape of the compartments, by recording the diffusion of water molecules in more than six directions (Basser et al., 1994; Basser & Jones, 2002; Le Bihan & van Zijl, 2002). DTI was previously shown to be a sensitive method for the study of WM connectivity, integrity, development and pathology (Basser et al., 1994; Dubois et al., 2006; Gupta et al., 2005; Huang et al., 2006; Hüppi & Dubois, 2006; Lebihan, 2006; Neil et al., 2002; Wakana et al., 2003).

2.2.1 Diffusion parameters

Several diffusion parameters describe the brain's microstructure, including the three diffusion tensor eigen values (λ_1, λ_2, λ_3), which represent diffusion along the three principal tensor axes, the mean diffusivity (MD) and mathematical measures of anisotropy.

The **mean diffusivity** (MD) is calculated as one third of the trace of the diffusion tensor:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \tag{1}$$

MD represents the overall magnitude of water diffusion independent of anisotropy. This parameter provides information on restriction and boundaries (i.e. the extent of packing/ density of cells), and is therefore a sensitive measure of brain maturation and/or injury (Alexander et al., 2007; Dubois et al., 2006).

Water diffusion anisotropy can be described by several parameters (Basser & Pierpaoli, 1996; Uluğ & van Zijl, 1999), of which **fractional anisotropy (FA**) is the most common. The FA parameter is calculated by dividing the magnitude of the anisotropic part of the diffusion tensor, by the magnitude of its isotropic part, resulting in a parameter that describes the degree of water diffusion anisotropy independent of the overall water diffusion coefficient (Basser & Pierpaoli, 1996):

$$FA(\lambda_1,\lambda_2,\lambda_3)=\frac{1}{\sqrt{2}}\sqrt{\frac{(\lambda_1-MD)^2+(\lambda_2-MD)^2+(\lambda_3-MD)^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}} \quad (2)$$

FA ranges between 0 (for perfectly isotropic diffusion; diffusion that is equal in all directions) and 1 (the hypothetical case of an infinite cylinder, i.e $\lambda_1 \ggg \lambda_2=\lambda_3$). A high FA value is detected in a dense and ordered structure such as in WM (Basser & Pierpaoli, 1996; Basser & Jones, 2002). This parameter is considered to reflect fiber density, axonal diameter, and myelination in WM (Alexander et al., 2007; Hüppi & Dubois, 2006).

The FA parameter is frequently used and appears to be quite sensitive to a broad spectrum of pathological conditions. Yet although many studies primarily focus on diffusion anisotropy, this may not be enough to characterize the tissue changes (Alexander et al., 2007). Since the FA value is calculated from the three eigenvalues, different eigenvalue combinations can generate the same FA value. For example, higher eigenvalues may indicate less maturation / myelinization and lower ones may indicate higher maturation, while in both cases the FA value may be reduced. Therefore, looking solely at the FA parameter can occlude trends that may be apparent in a specific eigenvalue. The eigenvalues of the diffusion tensor (axial diffusivity and radial diffusivity), are therefore important for the characterization of changes in the tissue microenvironment.

Axial diffusivity ($Da=\lambda_1$) represents the direction in which water diffusion is highest, which is typically parallel to WM fiber fascicles and is more strongly related to axonal morphology and degradation (Budde et al., 2009). Factors affecting axial diffusivity include buildup of cellular debris, breakdown of axonal structure, disordered microtubule arrangement, aggregation of filaments, and expansion of extracellular space (Schwartz et al., 2005).

Radial diffusivity ($Dr=(\lambda_2+\lambda_3)/2$) is the average value of the two small eigenvalues, and is considered to reflect the diffusivity orthogonal to the axonal bundles and to be mainly affected by the myelin in WM (Song et al., 2002).

2.2.2 Diffusion at high b values

The use of high b values (above > 3000 sec/mm²) requires a different data analysis approach which results in additional diffusivity parameters (Cohen & Assaf, 2002; Inglis et al., 2001; Ronen et al., 2005). Using high b values, several groups have reported multi-exponential decay of the MRI signal as a function of the b value, detecting signal from different tissue compartments, such as extracellular and intracellular (Inglis et al., 2001; Ronen et al., 2003). High b value DWI seems to be more sensitive to WM integrity than conventional DTI (Ronen et al., 2005) and was used in several studies including investigations of WM development in typically developing children (Ben Bashat et al., 2005; Cihangiroglu et al., 2009) and in young children with autism (Ben Bashat et al., 2007).

2.3 DTI and typical development

DTI has been widely used to describe WM development in children and adolescents (Cascio et al., 2007; Hüppi & Dubois, 2006; Rutherford et al., 1991; Sakuma et al., 1991). Reported changes are consistent across studies with an overall decrease in MD and an increase in FA with age (Barnea-Goraly et al., 2005; Cascio et al., 2007; Mukherjee et al., 2001). A decrease in all three eigen values was reported in newborns and infants from birth to childhood with a much higher rate of decline in the two smaller eigenvalues (Dr) than that of the largest eigenvalue (Da), resulting in an actual increase in FA (Hüppi et al., 1998; Mukherjee et al., 2001; Neil et al., 1998; Song et al., 2002).

The increase in anisotropy with age reflects increased organization of the nerve fibers. Relatively early DTI studies show that a large degree of anisotropy is already present in non-myelinated nerves (Beaulieu & Allen, 1994) or only poorly myelinated fibers such as in the WM of premature newborns (Hüppi et al., 1998; Neil et al., 1998). This increase has been attributed to changes in WM structure which accompany the "premyelinating state" (Wimberger et al., 1995) and are characterized by several histologic changes, including an increase in the number of microtubule-associated proteins in axons, a change in axon caliber, and a significant increase in the number of oligodendrocytes (Hüppi & Dubois, 2006). Following this stage, a continued increase in anisotropy is associated with the histologic appearance of myelin and its maturation (Huppi et al 1998; Huppi and Dubois 2006). These microstructural changes during development are not homogenous throughout the brain, showing considerable regional differences (Dubois et al., 2008; Hüppi & Dubois, 2006).

3. Brain development in autism - MRI findings

MR imaging studies have reported significant changes in GM and WM in subjects with autism compared to age-matched controls. Differences were detected in several brain regions both in the cerebrum and cerebellum (Amaral et al., 2008; Brambilla, 2003). However, it is important to emphasize that to date, all imaging results have been based on group analyses therefore it is not yet possible to make assumptions on an individual level.

3.1 Accelerated brain growth

One of the most consistent findings in autism research is increased brain volume during the first 2-3 years of life. The initial characterization of increased brain size and growth in autism relied heavily on head circumference data, later corroborated by structural MRI studies which established the correlation between head circumference and brain volume (Courchesne et al., 2001). Courchesne and colleagues, using retrospective head circumference records, found that brain volumes appeared normal for all children at birth. However, 2-3 year old children with autism had increased cerebral (18%) and cerebellar (39%) WM, and more cerebral cortical GM (12%) than controls (Courchesne et al., 2001). In contrast, older children and adolescents with autism did not exhibit enlarged gray and WM volumes. Based on these results, the authors hypothesized that overgrowth in autism is restricted to early childhood and followed by a period of abnormally slowed growth. Later studies supported these initial findings (Courchesne et al., 2004; Dementieva et al., 2005), although it was concluded that the increased brain volume was present in only about 70% of children with autism (Lainhart, 2006). This period of accelerated brain growth that occurs in the first years of life is parallel to the emergence of autistic symptoms. Both Courchesne's

early overgrowth theory and current research suggest that overgrowth is not ubiquitous to all regions of the brain. By 2-4 years of age, overgrowth is more evident in some regions and structures than others (Courchesne et al., 2005; Sparks et al., 2002), with the frontal lobes, temporal lobes, and amygdala being the sites of peak overgrowth (Sparks et al., 2002).
A few studies reported differences in older subjects with autism compared to controls. While there is converging evidence that autism is associated with enlarged brain volume early in development, evidence regarding the arrest of this overgrowth abnormality in adulthood are less conclusive demonstrating mixed results. Herbert et al. (Herbert et al., 2004), utilizing a WM parcellation technique, reported an enlargement in the radiate WM in all lobes, particularly in the frontal lobe in high functioning children with autism at a mean age of 9±0.9 years. Aylward (Aylward et al., 2002) reported significantly larger brain volumes in children with autism up to the age of 12 compared to controls, but no differences for individuals older than 12 years. In contrast, Piven and colleagues (Piven et al., 1996) did find significant enlargement in the temporal, parietal, and occipital, but not frontal lobes in 35 subjects with autism, with a mean age of 18 years. Another study reported decreased WM and GM volumes in children with autism at a mean age of 12±1.8, using a voxel-based analysis (McAlonan et al., 2005).

3.2 Volumetric changes in the corpus callosum

In contrast to the increased brain and cerebellar volume, the corpus callosum (CC) seems to be smaller in autism across all age groups (Boger-Megiddo et al., 2006; Stanfield et al., 2008). As the largest fiber connecting the two cerebral hemispheres, the CC has a central role in almost all networks and behaviors, including motor, sensory, visual, cognitive and limbic among other. While most researchers agree on the involvement of the CC in autism, the specific part of the CC which is affected is under debate. Piven and colleagues (Piven et al., 1997) detected smaller size of the body and posterior sub-regions of the CC in individuals with autism, at mean age 47.4 months, and reduced size of the CC only when adjusted for cerebral volume. Vidal et al (Vidal et al., 2006) reported reduction in both the splenium and genu of the CC in subjects with autism, mean age 10±3.3. In a recently published meta-analysis, reduced total CC area was detected in subjects with autism versus healthy controls (Frazier & Hardan, 2009), with the rostral body (Witelson subdivision 3) of the CC demonstrating the largest reduction in volume. Yet, other studies found no significant differences in the CC in adults with high functioning autism (Tepest et al., 2010).
Reduced size of the CC in autism has been demonstrated in contrast to the increased volume of WM which is mainly detected at young ages. Although this finding seems to be consistent in autism, it is non-specific. Reduced volume of the CC was also reported in many other disorders including attention deficit hyperactivity disorder (ADHD) (Giedd et al., 1994) and schizophrenia (Shenton et al., 2001). This leads us to question whether the pathology underlying this imaging abnormality is unique to autism or common to several disorders?

3.3 DTI findings in autism: review of published articles

This review of current published articles on DTI and autism was based on a search in Pubmed.gov performed on the 31st of March, 2011 (Table 1). The search criterion was "DTI and Autism", "DTI and ASD", "DWI and Autism" and "DWI and ASD". Only articles in English and those performed on humans were reviewed, a total of 25 articles. Two additional articles were retrieved from citations in the reviewed articles.

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Diffusion Tensor Imaging Studies in ASD

Study	Method	Diagnosis	Group; no.		Group; age, mean (SD) yr				
			Autism	Control	Autism	Control	FA	MD	Da
Barnea-Goraly et al. 2004	VB	HFA	7	9	14.6±3.4	13.4±2.8	↓	-	-
Keller et al. 2006	VB	HFA	34	31	18.97±7.3	18.97±6.2	↓	-	-
Alexander et al. 2007	Semi automated VOI	HFA, PDD-NOS	43	34	16.23±6.70	16.44±5.97	↓	↑	NS
Lee et al. 2007	Semi automated VOI	Autism, PDD-NOS	43	34	16.2±6.7	16.4±6.0	↓	↑	NS
Ben Bashat et al. 2007	High b value; ROI analysis	Autism	7	41	range: 1.8–3.3y	range: 4m-23y	↑	-	-
Catani et. Al. 2008	Tractography	Asperger	15	16	31±9	35±11	↓	NS	-
Thakkar et al. 2008	Surface based analysis	Autism, Asperger, PDD-NOS	12	14	30±11	27±8	↓	-	-

Table 1. DTI findings in autism

ASD;autism spectrum disorder,SD;standard deviation, FA;fractional anisotropy, MD;mean diffusivity, Da;axial diffusivity, Dr;radial diff
functioning autism, WM;white matter, CC;corpus callosum, IC;internal capsule, VOI/ROI;volume/region of interest, PDD-NOS;pervasiv
specified, NS;not significant, STG/STS;superior temporal gyrus/sulcus, PLIC;Posterior limb of the internal capsule, CP;cerebral peduncl

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Diffusion Tensor Imaging Studies in ASD									
Study	Method	Diagnosis	Group; no.		Group; age, mean (SD) yr				
			Autism	Control	Autism	Control	FA	MD	Da
Sundaram et al. 2008	Tractography	Autism, Asperger, PDD-NOS	50	16	4.79±2.43	6.87±3.45	↓	↑	-
Pugliese et al. 2009	Tractography	Asperger	24	42	23±12	25±10	NS	NS	-
Pardini et al. 2009	Tractography and VB	Autism	10	10	19.7 ± 2.83	19.9 ± 2.64	↓	-	-
Lee et al. 2009	VBM	HFA, PDD-NOS	43	34	16.23±6.70	16.44±5.97	↓	↑	-
Ke et al. 2009	VB	HFA	12	10	8.75±2.26	9.40±2.07	↓	-	-
Thomas et al. 2010	Tractography	HFA	12	18	28.5±9.7	22.4±4.1	NS	-	-
Lange et al. 2010	Semi automated VOI	HFA	30	30	15.78±5.6	15.79±5.5	↓	↑	↑

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Diffusion Tensor Imaging Studies in ASD									
Study	Method	Diagnosis	Group; no.		Group; age, mean (SD) yr				
			Autism	Control	Autism	Control	FA	MD	Da
Fletcher et al. 2010	Volumetric DTI segmentation	HFA	10	10	14.25±1.92	13.36±1.34	NS	↑	NS
Cheng et al. 2010	TBSS	ASD	25	25	13.71±2.54	13.51±2.20	↓or ↑ region dependent	-	↓or ↑ region dependent
Noriuchi et al. 2010	VB	HFA, Asperger	7	7	13.96±2.68	13.36±2.74	↓	-	↓
Shukla et al. 2010a	VOIs/ROIs	Autism, Asperger	26	24	12.7±0.6	13.0±0.6	↓	↑	↓
Shukla et al. 2010b	TBSS	Autism, Asperger	26	24	12.8±0.6	13.0±0.6	↓	↑	NS
Barnea-Goraly et al. 2010	TBSS	Autism	17	17 siblings 18 controls	10.5±2	8.9±1.9 9.6±2.1	↓	-	↓
Sahyoun et al. 2010	TBSS	HFA	9	12	12.8±1.5	13.3±245	↑	-	-

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ILF/SLF;inferior/superior longitudinal fasciculus

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Diffusion Tensor Imaging Studies in ASD									
Study	**Method**	**Diagnosis**	**Group; no.**		**Group; age, mean (SD) yr**				
			Autism	**Control**	**Autism**	**Control**	**FA**	**MD**	**Da**
Bloeman et al. 2010	VB technique	Asperger	13	13	39±9.8	37±9.6	↓	↓	-
Shukla et al. 2011	TBSS	Autism, Asperger	26	24	12.8±0.6	13.0±0.6	↓	↑	NS
Mengotti 2011	DWI VB and ROI	Autism	20	22	7±2.75	7.68±2.03	-	↓or ↑ Age dependent	-
Weinstein et al. 2011	Tractography and TBSS	Autism	22	32	3.2±1.1	3.4±1.3	↑	NS	NS
Groen et al. 2011	Kurtosis VB	HFA	17	25	14.4±1.6	15.5±1.8	NS	↑	-
Jou et al. 2011	Tractography and VB	ASD	10	10	13.06 ±9.85	13.94±4.23	↓	-	-

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ASD;autism spectrum disorder,SD;standard deviation,FA;fractional anisotropy, MD;mean diffusivity, Da;axial diffusivity, Dr;radial diffu functioning autism, WM;white matter, CC;corpus callosum, IC;internal capsule, VOI/ROI;volume/region of interest, PDD-NOS;pervasiv specified, NS;not significant, STG/STS;superior temporal gyrus/sulcus, PLIC;Posterior limb of the internal capsule, CP;cerebral peduncl ILF/SLF;inferior/superior longitudinal fasciculus

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Barnea Goraly and colleagues (Barnea-Goraly, 2004) were the first to apply DTI to a small number of children with autism and a control group using a voxel-based approach. They reported reduced FA in the CC and in the WM of the ventromedial prefrontal cortices, anterior cingulated gyri and temporoparietal junctions, indicating a reduction in WM integrity in the autism group. Following this auspicious start, most autism research to date has avoided early childhood studies, focusing instead on high functioning adolescents or adults with ASD, and focused mainly on FA and / or MD, to the exclusion of other diffusivity parameters. Most studies in these age groups reported reduced integrity of the WM in several brain regions including the limbic system, temporal and frontal lobes and CC.

Many studies were conducted in subjects from the entire ASD spectrum, including autism, Asperger's and PDD-NOS, i.e. a very heterogeneous group. Consistent findings in these studies were reduced FA in the CC (Alexander et al., 2007; Jou et al., 2011; Lee et al., 2009; Shukla et al., 2010, 2011b) in the superior temporal gyrus (Cheung et al., 2009; Lee et al., 2007, 2009; Shukla et al., 2011a); the anterior cingulate cortex (Cheng et al., 2010; Thakkar et al., 2008); the frontal lobe (Cheng et al., 2010; Shukla etl al., 2011a; Sundaram et al., 2008); the thalamus (Lee et al., 2009) and the interior and posterior limbs of the internal capsule (Cheng et al., 2010; Shukla et al., 2010).

Most studies conducted on subjects with high functioning autism or with Asperger's syndrome reported reductions in FA in the frontal and temporal lobes (Barnea-Goraly, 2004; Bloemen et al., 2010; Ke et al., 2009; Lange et al., 2010; Noriuchi et al., 2010); the limbic system (Bloemen et al., 2010; Noriuchi et al., 2010; Pugliese et al., 2009); the superior longitudinal fasciculus (Noriuchi et al., 2010); the CC (Bloemen et al., 2010; Keller et al., 2006; Noriuchi et al., 2010); and cerebellum (Catani et al., 2008). One study reported areas of reduced FA in children with high functioning autism (mean age 12.8 years) compared to controls, within the frontal WM and the superior longitudinal fasciculus, and increased FA within peripheral WM (Sahyoun et al., 2010). Three studies did not find any significant differences in FA values (Groen et al., 2011; Fletcher et al., 2010; Thomas et al., 2010).

And finally, studies conducted only in subjects with autism (subgroup, not the entire spectrum) reported reductions in FA in the frontal, parietal and temporal lobes (Barnea-Goraly et al., 2010); the frontal lobe (Mengotti et al., 2011; Pardini et al., 2009); and CC (Mengotti et al., 2011).

Nine of eleven studies that investigated axial and radial diffusivity, reported increased Dr along with increased MD and reduced FA in subjects with autism compared to controls (one study reported mixed results, region dependent). Five of these articles did not find significant results in Da, while another five reported mixed results (3 reported reduced Da, one region dependent, and one increased Da). Two studies reported reduced Da without significant results in Dr (see Table 1).

A few diffusion studies reported results in young children with autism (<6 years) (Ben Bashat et al., 2007; Mengotti et al., 2011; Sundaram et al., 2008; Weinstein et al., 2011). Two of these studies reported an opposite trend of increased FA values, in several brain regions. The first study, using high b value DWI, demonstrated an increase in FA values in the frontal lobe of 1.8-3.3 year old children with autism (Ben Bashat et al., 2007). Higher restriction was more dominant in the left hemisphere and was mainly detected in the frontal lobe, indicating abnormal density with regards to age. Higher restriction and increased FA values were also detected in the genu and splenium of the CC (the body of the CC was not

studied). In this study, it was suggested that early and accelerated abnormal maturation occurring in young subjects with autism supports brain overgrowth at these ages. In the second study, increased FA was detected in the genu and body of the CC (Witelson subdivision 3), left superior longitudinal fasiculus and right cingulum compared with age matched controls (Weinstein et al., 2011). Changes in FA reported in this study were mainly driven by a decrease in Dr. A third study (Mengotti et al., 2011) used DWI, and reported reduced MD in a restricted group of 7 children with autism (mean age 7.28 years old) in the frontal cortex, the genu and splenium of the CC. The fourth study performed at young ages included children from the entire spectrum, and reported inverse results of reduced FA in short range association fibers (Sundaram et al., 2008).

To sum up, several brain regions show structural differences between subjects with autism and controls. The reported regions form part of major networks relating to several behaviors that are recognized as core deficits in autism. These findings support the conception of autism as a connectivity disorder. The diversity of findings might be due to the numerous issues inherent in autism research in general, and imaging studies in particular, as well as age-related differences, which will be further discussed.

4. Abnormal developmental trajectories

Studies of young subjects with autism indicate increased FA which contrasts with findings of reduced FA in adolescents and young adults. This inconsistency seems to be age-related. The majority of autism imaging studies to date have been conducted on adolescents and young adults. Some studies present developmental curves of FA according to age, and extrapolation of this data points to increased FA at young ages, although most authors did not discuss these findings. A consideration of the data presented in the study by Lee et al, (Lee et al., 2007) (see Figure 2 in that manuscript), suggests that at younger ages (<12 years) there could be increased FA in the temporal stem relative to normal controls. A similar trend can be seen in another study (Shukla et al., 2011a) with extrapolated increased FA and reduced MD in children with autism younger than 8 years, in whole brain WM skeleton compared to controls (see Figure 3 in that manuscript). In a study performed by Cheng et al, (Cheng et al., 2010), FA was higher in children with autism below the age of ~13 years in several brain regions: the right paracentral lobule, right superior frontal gyrus and left superior longitudinal fasciculus (see Figure 3 in that manuscript). Mengotti et al (Mengotti et al., 2011) detected reduced MD in a restricted group of 7 children within the autism subgroup, mean age of 7 years, in the bilateral frontal cortex and in the left side of the genu of the CC.

A similar concern relating to the possibility of age dependency of other imaging measurements in autism can be seen in volumetric measurement, both of WM volume, such as in the frontal lobe and several GM structures. In both cases enlargement was found in young children with autism, while these differences were either not present or reversed in older subjects. GM volume in younger individuals with autism was larger for the amygdala (Sparks et al., 2002) and smaller in the cerebellar vermal lobules compared to controls. These findings were either less pronounced or were not present in older groups (Stanfield et al., 2008). Similar differences were detected in studies using event-related potentials (ERPs), detecting higher amplitude of response to unexpected novel event in subjects with autism compared to normal controls during childhood, and the opposite during young adulthood (Ferri, 2003).

In summary, higher FA and reduced MD were detected in young subjects with autism compared to controls. This pattern seems to be reversed above the age of 7-13 years when

reduced FA and increased MD are detected in subjects with autism compared to controls. In the age range of 7-13 there seems to be a period of "pseudo-normalization" of the FA and MD. Longitudinal studies are still needed to confirm this assumption, yet, studies that aim to compare subjects with autism to controls, at a specific age, are recommended not to focus on this age range, since significant results are less likely to be detected.

4.1 What is the pathology underlying abnormal white matter development?

Accelerated brain growth in young children with autism, as measured by volumetric studies, seems to coincide with increased FA and reduced MD, as detected by DTI. What leads to this deviant developmental trajectory? Could excessive prenatal neurogenesis, abnormal pruning or excessive dendrite growth be involved, resulting in aberrant connectivity and overall brain enlargement after birth? Or is there perhaps an increase of myelination or inflammatory response leading to excessive microglial activation? (Schumann & Nordahl, 2010). Post mortem and genetic studies support the combination of several cellular factors that account for autism pathology during early development (Morgan et al., 2010; Rubenstein, 2010; Schumann & Nordahl, 2010). Genetic studies reveal that a number of mutations converge on a common neurodevelopmental pathway involved in neurogenesis, axon guidance and synapse formation, all of which are critical for proper neural connectivity (Benvenuto et al., 2009; Geschwind, 2009). A recent post mortem study, detected microglial activation and increased microglial density in two thirds of their sample of young children (n=5, age < 6 years) (Morgan et al., 2010). An over expression of some or of a combination of these processes can explain the reduced MD and increased FA in young children with autism. Although FA seems to be highly sensitive to microstructural changes, it is less sensitive to the type of changes (Alexander et al., 2007). Changes in FA should therefore be interpreted with caution, and examining other diffusivity values may improve our understanding. Reduced Dr without significant change of Da was detected at a young age, accounting for the reduced MD and increased FA. Normal developmental studies, related reduction in Dr with the myelination process (Song et al., 2002). It is postulated therefore, that the reduced Dr in autism may express over-myelination at a young age. Another imaging study supports this finding (using T2 weighted), showing overdevelopment of WM in several brain regions in children with autism, which were considered to reflect myelination changes (Carmody & Lewis, 2010).

Therefore, it is hypothesized that accelerated-myelination contributes to brain overgrowth in young children with autism, probably along with other developmental processes. Is this finding unique to autism? Once again, findings are mixed. Previous studies in children with developmental delay showed reduced myelination, (Pujol et al., 2004). Reduced WM volume was detected in subjects with ADHD (Castellanos et al., 2002). In contrast, a study of children with developmental language disorder showed increased volume and later or longer-myelinating regions compared to controls, similar to autism findings (but not in all brain regions) (Herbert et al., 2004).

5. Why have we failed so far to find imaging biomarkers?

5.1 Imaging research in autism – only the beginning

Despite the developmental nature of the disorder, it seems that autism research focused on early childhood, while critical to our understanding of the nature of abnormal development, is still in the early stages. While evidence of accelerated brain growth during the first years

of life has been accumulating for over a decade, there has not been much progress in the interpretation of this finding. Most DTI studies in autism were performed on adults and adolescents, with just a few studies performed at young ages (<6 years). In addition, there are currently no post mortem studies on young children focusing on developmental trajectories which could shed light on the underlying pathology. Hence, future neuroimaging studies can contribute substantially to the understanding of the neurobiology of autism and, in particular, to the understanding of the important distinction between congenital pathology and acquired impairments.

A reduction in the age of diagnosis of ASDs, access to services and early intensive intervention are crucial for improving developmental outcomes (Dawson et al., 2010). Identification of imaging markers that may assist in early diagnosis is therefore of the utmost importance. In addition, studies of autism at young ages may be more sensitive to the origin of the disorder and may be less confounded by developmental changes, medication, seizures and more. Future studies should aim to identify imaging biomarkers with an emphasis on young ages.

5.2 Inherent problems in autism research

In most autism research, study populations vary widely, due to the heterogeneity of ASDs, as well as differences in diagnostic criteria, subject characteristics (including age, IQ, etc.) and research methodologies. These core issues no doubt account for some of the diversity in results reported in the literature and the failure to find any biomarker, as yet.

The definition of autism is the first and probably the major problem. ASD is a category that includes autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger's syndrome, disintegrative disorder and Rett syndrome. Considerable debate exists as to whether conditions at the higher functioning end of the autistic spectrum (i.e., high functioning autism, Asperger's syndrome, and PDD-NOS) are separate disorders or simply different expressions of the same underlying condition (Macintosh & Dissanayake, 2004; Matson, 2007).

In addition, there is a wide developmental and behavioral heterogeneity within each group in the spectrum with wide ranging symptoms (S.E. Levy et al, 2009). Some children display signs of developmental delay within the first 18 months of life, however, 25-40% of children with autism initially demonstrate near-normal development until 18-24 months, when they regress into an autism that is generally indistinguishable from early onset autism (Ozonoff et al., 2008). Some children develop language while others remain non verbal; some display interest in social interaction while others remain secluded; some manifest repetitive or obsessive compulsive behavior patterns while others do not; some respond well to therapeutic intervention while others show limited progress (Ben-Itzchak & Zachor, 2007; Charman et al., 2011; Luyster et al., 2008; Pelphrey et al., 2011).

Furthermore, co–morbidity is highly prevalent in ASD. For example, 40-75% of children with ASD are mentally retarded (Fombonne, 2003; Newschaffer et al., 2007) and epilepsy is reported in up to one third of children (Jeste, 2011). Several genetic diseases have also been associated with autism including Fragile-X and Tuberous sclerosis complex (Benvenuto at al., 2009).

Protocol parameters and the various image processing approaches used in imaging studies, may also affect results. Some studies used volume of interest definition, either by manual selection or using reconstruction of a specific fiber bundle (i.e. fiber tractography) while

others used whole brain comparison (including voxel based DTI analysis and tract-based special statistics (TBSS)). Several inherent differences between these two approaches may account for some of the contrasting results reported in the literature (Alexander et al., 2007).

5.3 Is studying autism as a syndrome the right direction?

Autism has diverse clinical manifestations, behavioral phenotypes, developmental dimensions and genetic origins, all of which complicate research and clinical practice with regard to etiology, the selection of appropriate interventions and the search for biomarkers. Most DTI studies in autism were performed on high functioning subjects, since scanning subjects with low functioning disorders is more difficult. It is therefore debatable whether similar findings can be expected among these heterogeneous groups and whether any conclusions can be drawn about the whole spectrum or generalized to other groups, based on findings in one particular group.

Recently Happe et al (Happé et al., 2006) argued that attempts to propose a unified account of autistic symptoms failed at all levels of analysis – genetic, imaging and behavioral. Bearden & Freimer (Bearden & Freimer, 2006) claim that the inherent imprecision of behavioral phenotyping is probably the most important factor contributing to the failure to discover the biological factors involved in psychiatric and neurodevelopmental disorders. In a recent review article, Levy and Ebstein (Y. Levy & Ebstein, 2009) argue that syndrome heterogeneity, cross-syndrome similarities and syndrome comorbidities challenge the relevance of syndromes to biological research, and that cohort selection based on cross-syndrome trait classification would be more accurate than based on syndromic groups.

6. Conclusions

In summary, current theories of neural deficiencies in autism emphasize the first few years of life as a key period when abnormalities in the development of neural circuitry occur, along with the first behavioral signs of autism. These abnormalities, which can be detected on the basis of group differences, persist into adulthood. Despite recent advances in autism research, early childhood neuroimaging studies are few and far between, hindering investigation of the developmental nature of autism. Thus the specific relationship between etiology, mechanisms, genetic and imaging markers and the ensuing behavioral abnormalities remains unclear.

Abnormal trajectories in WM development in autism, resulting in impaired connectivity, have been demonstrated by imaging studies. While several mechanisms may account for the increased brain volume in young children, DTI can detect microstructural changes and might help to reveal the neurobiology underpinning autism. Based on recent findings, it is suggested that accelerated myelination might be one of the processes occurring at a young age in subjects with autism.

Subjects with autism exhibit changes in diffusivity values with age. Higher FA values along with reduced MD were detected in young children with autism, while reduced FA and increased MD were reported at older ages. The shift of FA from higher to lower values results in a period of suggested "pseudo-normalization" which seems to occur between the ages of 7-13 years. This hypothesis accounts for the seemingly controversial results detected in young children versus adolescents and young adults.

There are many contrasting reports regarding the location of abnormalities within the brain of subjects with autism, both during adolescence and at younger ages. This might support

asynchrony in maturational processes in different brain regions which may be the basis for abnormal connectivity and behavior. Studies performed at young ages may be able to detect congenital neurobiological pathologies and distinguish these from acquired impairments that are more likely to be detected at older ages.

Longitudinal studies in a large cohort may be the best way to solve the autism puzzle. Integrating several approaches, including genetic, postmortem and imaging, may be the only way to provide answers concerning the neuropathology of autism (Schumann & Nordahl, 2010). In addition, a multimodal approach in imaging studies, which has demonstrated major advantages in several brain pathologies and in a recently published study of autism (Ecker et al., 2010), should be incorporated in future studies.

Future research should focus on subgroups with specific traits of the autistic disorder, or endophenotypes such as language impairment, in order to provide promising avenues for understanding the neurobiological processes underlying autism. Future studies will reveal whether differences are detectable on an individual basis; whether imaging results can be powerful enough to be included in the diagnostic criteria of autism; and whether reported imaging findings are specific enough to differentiate autism from other developmental disorders.

7. Acknowledgment

I am indebted to Maya Weinstein, Moran Artzi, and Reut Granot Halevi, for their helpful assistance in preparing this chapter; Vicki Myers for editorial assistance; Yonata Levy, Liat Ben Sira, Talma Hendler, Ditza Zachor and Esti Ben Itzhak for being part of our group searching for imaging clues in the puzzle of autism; March of Dimes for partially supporting our research; and last but not least, to the children and their families who so willingly collaborated.

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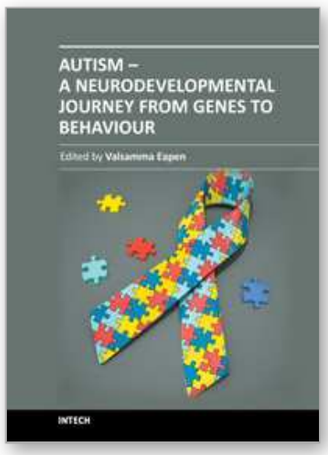

Autism - A Neurodevelopmental Journey from Genes to Behaviour
Edited by Dr. Valsamma Eapen

ISBN 978-953-307-493-1
Hard cover, 484 pages
Publisher InTech
Published online 17, August, 2011
Published in print edition August, 2011

The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

How to reference
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Dafna Ben Bashat (2011). Abnormal Developmental Trajectories of White Matter in Autism - The Contribution of MRI, Autism - A Neurodevelopmental Journey from Genes to Behaviour, Dr. Valsamma Eapen (Ed.), ISBN: 978-953-307-493-1, InTech, Available from: http://www.intechopen.com/books/autism-a-neurodevelopmental-journey-from-genes-to-behaviour/abnormal-developmental-trajectories-of-white-matter-in-autism-the-contribution-of-mri

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