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REVIEW ARTICLE

White matter microstructure in fetal alcohol spectrum disorders: A systematic review of diffusion tensor imaging studies

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Abstract

Diffusion tensor imaging (DTI) has revolutionized our understanding of the neural underpinnings of alcohol teratogenesis. This technique can detect alterations in white matter in neurodevelopmental disorders, such as fetal alcohol spectrum disorder (FASD). Using Prisma guidelines, we identified 23 DTI studies conducted on individuals with prenatal alcohol exposure (PAE). These studies confirm the widespread nature of brain damage in PAE by reporting diffusivity alterations in commissural, association, and projection fibers; and in relation to increasing cognitive impairment. Reduced integrity in terms of lower fractional anisotropy (FA) and higher mean diffusivity (MD) and radial diffusivity (RD) is reported more consistently in the corpus callosum, cerebellar peduncles, cingulum, and longitudinal fasciculi connecting frontal and temporoparietal regions. Although these interesting results provide insight into FASD neuropathology, it is important to investigate the clinical diversity of this disorder for better treatment options and prediction of progression. The aim of this review is to provide a summary of different patterns of neural structure between PAE and typically developed individuals. We further discuss the association of alterations in diffusivity with demographic features and symptomatology of PAE. With the accumulated knowledge of the neural correlates of FASD presenting symptoms, a comprehensive understanding of the heterogeneity in FASD will potentially improve the disease management and will highlight the diagnostic challenges and potential areas of future research avenues, where neural markers may be beneficial.

KEYWORDS

diffusion tensor imaging, fetal alcohol spectrum disorders, fetal alcohol syndrome, prenatal alcohol exposure, white matter

1 | INTRODUCTION

Maternal alcohol consumption during pregnancy can permanently damage the developing craniofacial structure of a fetus. This may result in a wide spectrum of physiological, cognitive, and neurobehavioral outcomes (Barr & Streissguth, 2001; Crepin, Dehaene, & Samaille, 1989; Hill, Hegemier, & Tennyson, 1989). Fetal alcohol syndrome (FAS), associated with growth deficiencies, abnormal facial features, and evidence of CNS dysfunction, is only a tip of an iceberg in teratogenic effects of alcohol. The wide array of diagnosable adverse neurophysiological outcomes of prenatal alcohol exposure (PAE) is labeled as fetal alcohol spectrum disorder (FASD). This term signifies the diverse phenotype of this syndrome among affected individuals (Malisza et al., 2005). Several attempts have been made to understand the structural brain abnormalities underlying cognitive and behavioral deficits in PAE. Autopsies of infants with severe PAE have detected the very first macro scale brain anomalies, including agenesis of the corpus callosum, microcephaly, ventriculomegaly, and a small cerebellum (Clarren & Smith, 1978; Peiffer, Majewski, Fischbach, Bierich, & Volk, 1979). Although autopsy studies can be informative, they are inevitably limited by the low number of cases, and typically contain only the most severe alcohol-affected cases that die during infancy.

Novel neuroimaging methods have dramatically improved our knowledge about the teratogenic effects of alcohol in vivo and have revealed the presence of more subtle changes in neural networks, far beyond the current clinical criteria used to diagnose FASD. These methods have demonstrated a wide array of structural (Archibald et al., 2001; Autti-Ramo, 2002; Mattson et al., 1996), functional, and metabolic abnormalities (Guerri, Bazinet, & Riley, 2009; Roussotte, Soderberg, & Sowell, 2010) in individuals with PAE, which depend on the timing, amount, and frequency of alcohol consumption, as well as genetics and other prenatal and postnatal environmental factors (Guerri, Bazinet, & Riley,, 2009). In this context, the development of diffusion tensor imaging (DTI) has substantially facilitated the in vivo characterization of neural macro- and microstructure especially of the white matter.

In brain tissue, mater movement is restricted by cell membranes, myelin sheath, organelles, or macromolecules. DTI measures water diffusion, and the structure of the local environment can be inferred by the restrictions caused by water movement. This can provide sensitivity to changes in the neural structure such as myelination, axon orientation, and axonal packing (Basser & Jones, 2002). Fractional anisotropy (FA), the most commonly used diffusion metric, is an indirect index of the amount of directionality. FA shows white matter maturation as it increases through the developmental process (Huppi et al., 1998). It also correlates positively with better performance on cognitive domains (Nagy, Westerberg, & Klingberg, 2004; Schmithorst, Wilke, Dardzinski, & Holland, 2005), and tends to reduce by neurodegenerative processes (Agosta, Galantucci, & Filippi, 2017). Thus, it is claimed that FA is a biomarker of white matter integrity, although it does not specifically determine the microstructural features (Alexander, Hasan, Kindlmann, Parker, & Tsuruda, 2000). Mean diffusivity (MD) reflects the total amount of water movement in a voxel regardless of direction. It is higher in areas where water diffuses freely (e.g., cerebrospinal fluid) and lower in areas of high tissue density (e.g., white and gray matters). MD values tend to decrease with maturation due to reduced extracellular spaces in the myelinated white matter (Beaulieu, 2002; Engelbrecht, Scherer, Rassek, Witsack, & Modder, 2002). Alterations in white matter integrity due to developmental or acquired defects typically contribute to higher MD values compared with the intact white matter (Neil, Miller, Mukherjee, & Huppi, 2002). Two additional measures of axial diffusivity (AD) and radial diffusivity (RD), which are simply the diffusivity parallel and perpendicular toward membranes, respectively, more specifically express the underlying pathology. Investigations have related AD with axonal damage and fragmentation, while RD has been linked to the integrity of myelin (Aung, Mar, & Benzinger, 2013; Concha, 2014; Song et al., 2002). However, this distinction is challenged by evidence of changes in RD followed by changes in axonal packing density, axonal diameter, and neuroinflammation (Wheeler-Kingshott & Cercignani, 2009).

In this review, we summarize the DTI findings of white matter correlates of PAE compared with typically developed (TD) individuals. Since there is a great variability in neural structure among individuals with PAE, we further discuss the neural damage in relation to physical and cognitive features. We also take into account the developmental trajectories of white matter and bimodal sex-specific pattern in this regard.

2 | SEARCH STRATEGY AND DATA EXTRACTION

We performed a systematic literature search based on the PRISMA framework (http://www.prisma-statement.org). MEDLINE and EMBASE databases were searced in March 2018 to identify the studies relevant to the application of DTI in prenatally exposed human individuals to alcohol, using this search terms: ("Fetal Alcohol Spectrum Disorders"[Mesh] OR Fetal Alcohol Spectrum Disorders [tiab] OR FASD [tiab] OR FASDs [tiab] OR Partial Fetal Alcohol Syndrome [tiab] OR Alcohol-Related Birth Defects [tiab] OR Alcohol Related Birth Defects [tiab] OR Birth Defects, Alcohol-Related [tiab] OR Alcohol Related Neurodevelopmental Disorder [tiab] OR FAE [tiab] OR Fetal Alcohol Effects [tiab] OR FAEs [tiab] OR Fetal Alcohol Effects [tiab] OR Fetal Alcohol Syndrome [tiab] OR Syndrome, Fetal Alcohol [tiab]) AND ("Diffusion Tensor Imaging" [Mesh] OR Diffusion Tensor Imaging [tiab] OR Diffusion Tractography [tiab] OR DTI [tiab] OR TBSS [tiab] OR tract-based spatial statistics [tiab] OR tractography [tiab] OR fractional anisotropy [tiab] OR diffusion tensor MRI [tiab] OR ("White Matter" [Mesh] OR White Matter [tiab] OR White Matter microstructure [tiab] OR White Matters [tiab]) OR ("Corpus Callosum"[Mesh] OR Callosum[tiab] OR Callosums [tiab] OR Neocortical Commissure[tiab] OR Neocortical Commissures [tiab] OR Interhemispheric Commissure [tiab])). No time limit was set and there were no language restrictions. Results were imported to Covidence software (https://www.covidence.org). Articles were screened by two investigators (M.H.A and M.H.Y). All titles and abstracts from the retrieved articles were screened and full texts of potentially eligible articles were obtained. To ensure that our systematic review did not miss any items, reference lists of identified articles were searched for additional studies by F.G.S. and M.H.Y. We included only full text articles of any design which used DTI to investigate neural structure in human subjects with PAE with (including all subtypes) or without a diagnosis of FASD. Methodological quality of the included case–control studies was assessed using the modified Newcastle Ottawa Scale (Stang, 2010).

3 | RESULTS

Our search strategy initially yielded a total of 374 articles. After eliminating duplicates, 228 articles were screened by title and abstract for eligibility. Twenty-four articles were selected for full-text evaluation, of which one article was excluded, as it was focused on multidrug exposure without sufficient details about alcohol exposure. In total, 23 full-articles were included in this review, of which one study is longitudinal, 20 studies are case–control and 2 studies are case series in design. Table 1 summarizes these studies regarding demographic data of participants, imaging technical information, and significant imaging findings divided into (1) between-group differences of PAE versus TD, and (2) the correlation of DTI metrics with symptomatology of FASD including cognitive decline, facial dysmorphology, and with the extent of PAE and FASD severity.

The methodological quality of the included studies is overall good, receiving between 6 and 8 stars in the Newcastle Ottawa Scale

TABLE 1 An overview of the literature

		Demographic features						
	Study	Country of origin	FASD subgroup studied	*n*[a] of cases (males)	*n* of TD (males)	Age range in years	Mean age in years (case)	Mean age in years (TD)
1	Ma et al., 2005	USA	FAS (African American, low SES, MR)	9 (5)	7 (2)	18–22	20 ± 2	21 ± 1
2	Wozniak et al., 2006	USA	Relatively mild FASD (pFAS, ARND, static encephalopathy; excluded: FAS, MR, microcephaly and exposure to other drugs except tobacco, major psychiatric disorders)	13 (7 or 6[b])	13 (6)	10–13	12.3 ± 0.97	12.4 ± 1.2
3	Sowell et al., 2008	USA	FAS/pFAS/ARND	4/5/9 (9)	19 (8)	7–15	10.525 ± 2.714	11.238 ± 2.805
4	Lebel et al., 2008	Canada	FAS/neurobehavioral disorder/static encephalopathy/neurobehavioral disorder with sentinel physical findings/FASD	2/6/3/2/11 (13)	95 (50)	5–13	9.1 ± 2.2	9.8 ± 2.2
5	Fryer et al., 2009	USA	Heavy PAE Nondys/Dys (Rt handed)	6/6 (?[b])	12 (6)	8–18	13.85 ± 3.11	13.18 ± 2.94
6	Li, Coles, Lynch, & Hu, 2009	USA	PAE Dys/Nondys (African American, low SES)	28/29 (12/6)	25 (12)	19–27	22.9 ± 2/23.0 ± 1.8	22.8 ± 1.71
7	Wozniak et al., 2009	USA	FAS/pFAS/static encephalopathy (excluded if not heavy PAE, VLBW or other prenatal drug exposure except nicotine and caffeine)	8/23/2 (18)	19 (12)	10–17	12.6 ± 2.2	12.6 ± 2.2
8	Lebel, Rasmussen, Wyper, Andrew, & Beaulieu, 2010	Canada	FAS/pFAS/neurobehavioral disorder/static encephalopathy/neurobehavioral disorder with sentinel physical findings/static encephalopathy with sentinel physical findings	2/1/10/4/1/3 (12)	No control	5–13	9.2 ± 2.2	No control
9	Santhanam et al., 2011	USA	PAE Nondys/Dys (L–handed, predominantly African–American, low SES)	28/29 (?)	25	18–24	22.9 ± 1.7/23.0 ± 2.1	22.8 ± 1.7
10	Spottiswoode et al., 2011	South Africa	Rt handed heavy PAE (FAS and pFAS)	10 (?)	11 (?)	9.7–13.7	26.5 ± 5.4	25.2 ± 3.4
11	Wozniak et al.,	USA	FAS/pFAS/other FASD including sentinel physical findings and static encephalopathy (excluded if not heavy PAE, VLBW, or other prenatal drug exposure except nicotine and caffeine, cocaine, marijuana)	1/11/9 (12)	23 (13)	10–17	13.9 ± 2.3	12.8 ± 2.4
12	Colby et al., 2012	USA	PAE (exposed, ARND, sentinel [shows mild facial dysmorphology], pFAS, FAS); more than 5 years old, IQ > 70	19 (11)	27 (11)	Not mentioned	10.79 ± 2.32	10.30 ± 3.35
13	Treit et al., 2013	Canada	FASD (FAS/pFAS/static encephalopathy/NBD–AE/ARND/FASD)	2/3/3/7/1/1 (11)	27 (15)	5–15	8.2 1.8 at first scan, 11.4 2.1 at last scan, scanned 1.8–4.2 years apart	8.5 1.6 at first scan, 12.0 1.8 at last scan, scanned 1.8–4.2 years apart
14	Green, Lebel, Rasmussen, Beaulieu, & Reynolds, 2013	Canada	FASD (FAS/neurobehavioral disorder/static encephalopathy/sentinel physical findings/static encephalopathy)	1/8/3/2 (8)	No control	8–13	10 ± 1.6	No control

(*Continues*)

TABLE 1 (Continued)

	Demographic features						
	Study	Country of origin	FASD subgroup studied	*n*[a] of cases (males)	*n* of TD (males)	Age range in years	Mean age in years (case)	Mean age in years (TD)
15	Paolozza et al., 2014a, Paolozza et al., 2014b	Canada	FAS/PFAS/ARND	3/9/31 (23)	35 (14)	7–18	12.3 ± 3.1	12.5 ± 3.0
16	Fan et al., 2016	South Africa	FAS/pFAS/heavily exposed nonsyndromal group (Rt handed)	11/17/29 (?)	24 (?)	Not mentioned	9.7 ± 1.1/9.4 ± 0.2/10.6 ± 1.1	10 ± 0.8
17	Taylor et al., 2015	South Africa	PAE newborns	11 (5)	9 (6)	36–44 wpost conception	2.6 ± 1.5 postpartum w, 41.2 ± 2.3 w post conception	3 ± 1.6 w postpartum, 41.6 ± 2.1 post conception
18	Donald et al., 2015	South Africa	Moderate to heavy PAE (other drugs excluded)	28 (13)	28 (19)	2–4 w postpartum	38.36 ± 1.81 w post conception	38.5 ± 1.8 w post conception
19	O'Conaill et al., 2015	Canada	ARND	20 (?)	21 (?)	10–14	12.20 ± 1.64	12.60 ± 1.29
20	Fan et al., 2016	South Africa	FAS/pFAS/nonsyndromal heavily exposed (Rt handed)	7/19/15 (21)	13 (7)	Not mentioned	FAS, pFAS: 10.4 ± 0.5; heavily exposed: 10.5 ± 0.3	10.4 ± 4
21	Paolozza, Treit, Beaulieu, & Reynolds, 2017	Canada	FAS/pFAS/ARND/PAE	4/12/36/17 (33)	67 (27)	5–18	12.5 ± 3.2	12.1 ± 3.2
22	Treit et al., 2017	Canada	FASD (FAS/pFAS/ARND or FASD)	10/6/54 (40)	74 (38)	5–32	14 ± 6 years	13 ± 5 years
23	Uban, Herting, Wozniak, & Sowell, 2017	USA	Moderate to heavy PAE	31 (16)	30 (15)	9.3–16	Boys: 12.3 ± 1.6 Girls: 12.7 ± 1.6	Boys: 12.9 ± 1.7 Girls: 13.3 ± 1.6

Imaging methodology					
Field strength	b values (sec/mm^2)	DTI analysis method	Regions/tracts studied	Toolbox	Other modalities
3 T	1,000	Manually defined tractography/ROI	gCC and sCC	DtiStudio	T1 (volumetry)
3 T	1,000	Manually defined tractography/ROI	6 regions of CC: gCC, rostral body, ant midbody, post midbody, iCC, sCC	FSL	T1 (volumetry)
1.5 T	1,000	VBA/ROI	Bilateral anterior and posterior temporal lobe, bilateral splenium, brainstem	FSL/SPM	T1 (white matter density)
1.5 T	1,000	Semiautomated tractography for 10 WM/ROI for 4 deep GM	WM: gCC, bCC, sCC, ILF, SLF, IFO, SFO, cingulum, UF and CST; GM: thalamus, globus pallidus, putamen, and head of caudate nucleus	SPM/ExploreDTI	T1 (volumetry), T2, FLAIR (gross anomalies)
3 T	2,000	TBSS/ROI	CC	FSL/AFNI	Volumetry
3 T	1,000	TBSS/ROI	6 regions of CC: gCC, rostral body, ant midbody, post midbody, iCC, sCC	FSL	None
3 T	1,000	Manually defined tractography/ROI	6 regions of CC: Ant portion of gCC, post portion sCC, sup portion of mid-body, inf portion of gCC and sCC, boundary between gCC and rostral body	FSL	None
1.5 T	1,000	VBA/tractography	Whole brain WM	SPM/ExploreDTI	T1, T2, and FLAIR to ensure there are no frank lesions
3 T	1,000	TBSS/ROI	Cingulum	FSL	fMRI
3 T	1,000	VBA/ROI	Cerebellar peduncles	FSL/SPM	None
3 T	1,000	Manually defined tractography/ROI	7 regions of CC: Rostrum, gCC, rostral body, ant mid-body, post mid-body, iCC, sCC	FSL	fMRI
1.5 T	1,000	TBSS/ROI	Whole brain WM	FSL	None
1.5 T	1,000	Semiautomated tractography	gCC, bCC, sCC, IFO, SFO, UF, ILF, SLF, cingulum, CST, ALIC	ExploreDTI	T1 (volumetric)
1.5 T	1,000	VBA, tractography	Whole brain WM	SPM	None
1.5 T at one site/3 T at two sites	1,000	Tract-specific/ROI	6 regions of CC: gCC, rostral body, ant mid-body, post mid-body, iCC, sCC	ExploreDTI	None

TABLE 1 (Continued)

Imaging methodology					
Field strength	**b values (sec/mm^2)**	**DTI analysis method**	**Regions/tracts studied**	**Toolbox**	**Other modalities**
3 T	1,000	VBA/ROI	Cerebellar peduncles	FSL	None
3 T	1,000	Probabilistic tractography/ROI	Three major WM classes through five networks: One transcallosal, including CC and corona radiata, B-projection fibers and B-association fibers	AFNI	Volumetry
3 T	1,000	TBSS/ROI	SLF, SFO, UF, cerebellar peduncles, CST, cerebral peduncle, post thalamic radiation, fornix, cingulum, CC	FSL	None
3 T	1,000	TBSS	Whole brain WM	FSL	fMRI
3 T	1,000	VBA/ROI	Whole brain WM	FSL	None
1.5 T at one site and 3 T at 3 sites	1000	Semiautomated tractography	gCC, bCC, sCC, ILF, SLF, IFO, cingulum, CST, UF	ExploreDTI	None
1.5 T	1,000	Semiautomated tractography	gCC, bCC, sCC, IFO, SFO, UF, ILF, SLF, cingulum, CST	ExploreDTI	T1 (cortical thickness and regional brain volumes)
3 T	1,000	TBSS/ROI	Cingulum, CST, SFO, IFO, optic radiation, SLF, UF, callosal body, fornix	FSL	None

Between-group findings (cases vs. TD)			
FA reduction	**MD increase**	**RD or AD alterations**	**Additional imaging results**
gCC and sCC	gCC and sCC	Not investigated	FA of sCC higher than that of gCC and MD of sCC lower than that of gCC, in both FAS and TD. No significant difference of intracranial volume and gCC, sCC, and entire CC morphology.
....	iCC	Not investigated	Trend toward smaller total brain volume, significantly smaller GM and CSF volume. No significant group differences in WM volume. After adjusting GM and WM volumes for cerebral volume, only a trend-level difference in GM volume between groups.
Lateral sCC (medial superior parietal WM), post cingulum, deep WM of R-temporal lobe, ILF, IFOF, R-internal capsule, brainstem regions	Not investigated	Not investigated	Lower WM density in the lateral sCC bilaterally and in R-deep temporal association fibers. Little overlap between FA and WM density differences in the more anterior portions of R-temporal lobe and more lateral aspects of the sCC where only FA differences were observed.
sCC, R-cingulum, ILF, SLF, L-thalamus **(higher FA in Globus pallidus)**	IFOF, L-ILF, R-CST, Globus pallidus, R-putamen, R-thalamus (trend toward elevated MD in the R-UF), **(lower MD in gCC)**	Higher RD in sCC, R-cingulum, ILF, SLF, L-thalamus	Reduced total brain, GM and WM volumes. WM volume slightly more affected.
TBSS: Ant and post corona radiata, R-SLF, UF, FOF, forceps major (findings most prominent in medial portions of the frontal and occipital lobes) ROI: bCC, **(higher FA in R-PLIC and R-cingulum)**; dysmorphic < nondysmorphic: bCC	L-ALIC, WM lateral to L-ant corona radiata, **(lower MD in R-ant corona radiata, and R-forceps major)**	Not investigated	Similar whole brain volume and GM + WM tissue volume.
TBSS: Dys < TD: iCC and its connected callosal fibers (trend in gCC and sCC) ROI: Dys<Nondys<TD: iCC	...	ROI: Dysmorphic > TD: RD in iCC	...
Posterior mid-body of CC, iCC, sCC (trend in gCC).	...	Not investigated	...
No control	No control	No control	...
Cingulum	Dysmorphic vs. TD: Cingulum	Higher RD in cingulum	DMN deactivation: Dys < Nondys < TD, suggesting higher PAE with more attention disruption.
L-MCP	...	Higher RD in L-MCP	...
Not investigated	Not investigated	Not investigated	Decreased interhemispheric connectivity in FASD.
(trend in external capsule and R-deep temporal WM)	...	...	PAE vs. PAE+ methamphetamine exposure and within a small subset of subjects matched exactly on alcohol exposure clinical severity: Lower FA in

(*Continues*)

TABLE 1 (Continued)

Between-group findings (cases vs. TD)			
FA reduction	**MD increase**	**RD or AD alterations**	**Additional imaging results**
			frontal and temporal areas bilaterally—Most prominently in the right external capsule
SFO; significant age-related increases of FA in 11/11 WM in TD and 8/11 in FASD (with exception of ILF, UF, and bCC)	gCC, UF (only in second scan); significant age-related decreases of MD in 9/11 (except SFO, CST) in FASD and 7/11 WM in TD (except SFO, CST, bCC, IFO); greater longitudinal decreases of MD between scans in FASD in SLF, SFO and IFO.	Greater longitudinal decreases of RD in FASD in IFO and SFO.	Significant effect of group on volume for all structures measured (whole brain, WM, cortical GM, thalamus, caudate, putamen, Globus pallidus, hippocampus, and amygdala), with 7–18% reductions in FASD compared with TD. Total brain volume added as a covariate, cortical GM, WM, thalamus, putamen and Globus pallidus volumes remained significantly reduced in FASD. Significant age-related increases of total brain, WM, Globus pallidus and amygdala volumes in TD and cortical GM in FASD. No significantly different proportions of subjects who underwent increases, no change, or decreases in volume between scans in the FASD vs TD.
No control	No control	No control	…
…	sCC	Higher AD in sCC	FA and MD of sCC increased with increasing age in both TD and FASD.
FAS < pFAS < TD: B-SCP	FAS and pFAS > TD: L-MCP pFAS > TD: R-ICP (no longer statistically significant after adjustment for child's age at scan)	…	…
…	**(lower MD in R-association network)**	Lower AD in transcallosal, R-association and R-projection fibers; lower RD in R-association fibers	No difference in total intracranial volume, WM volume and WM fraction.
…	…	Lower AD in R-SLF	Head circumference positively correlated with FA, and negatively correlated with MD, AD, and RD across groups in all WM tracts.
R-ILF	ILF, SLF, CC, CST, cingulate, UF, IFOF, Ext cap, sup corona radiata, arcuate fasciculus; and frontal, frontocentral, and central association fibers.	Not investigated	ARND showed greater activation of dorsal and ventral attention pathways in single-feature search compared with TD and ADHD, and lower activation in ARND during feature-conjunction task compared with single feature task
FAS, pFAS < TD: B-ILF, sCC, iCC Heavy PAE < TD: L-ILF and sCC	FAS, pFAS > TD: B-ILF, sCC, iCC, R-SLF, B-CST Heavy PAE > TD: iCC, sCC, L-ILF, R-CST	FAS, pFAS > TD: RD in L-ILF, sCC, iCC, R-SLF, CST Heavy PAE > TD: RD in L-ILF, sCC, iCC, Rt CST	…
PAE < TD: gCC, bCC, sCC, L-cingulum, R-CST, L-SLF, L-UF PAE females < TD females: gCC, L-SLF and L-UF Females < males: L-CST TD males < TD females: R-ILF	PAE > TD: L-UF	Not investigated	…
…	…	Not investigated	Reduced volume of nearly all structures (total brain [excluding CSF and cerebellum], WM, cortical GM, thalamus, caudate, putamen, Globus pallidus, hippocampus except amygdala) and thinner cortical thickness in middle frontal, inf occipital, lingual, fusiform, middle, and inf temporal gyri in FASD versus TD. Decrease in volume with age in both groups in cortical GM, putamen and Globus pallidus volumes. Thinner cortex at older ages in both groups. Steeper age-related increases of volume of WM and amygdala, and cortical thickness in gyrus rectus in TD than FASD. In both groups larger volumes of total brain, cortical GM, WM Globus pallidus, hippocampus and amygdala and thicker cortical thickness in occipital, lingual, temporal gyri, calcarine fissure, and surrounding cortex and insula in males than females. Magnitude of group differences (FASD and controls) greater among males than females in volume of thalamus, caudate, putamen and cortical thickness of fusiform gyrus.
PAE girls < TD girls: IFOF, UF; **PAE boys > TD boys: bCC, cingulum, CST, optic radiation, SLF**	…	Not investigated	–

Symptomatology correlations with DTI metrics	
Investigated cognitive domain, facial dysmorphology, FASD severity, or amount of PAE related to WM integrity	**Significant associations**
Correlation of FA and MD in gCC and sCC with dysmorphia and cognition (FSIQ, and visuomotor performance assessed by processing speed)	Lower FA of gCC correlated with lower FSIQ and processing speed scores only in TD
Correlation of total cerebral volume and MD of iCC with dysmorphia	–
Correlation of FA and white matter density within 7 ROIs (bilateral anterior and posterior temporal lobe, bilateral splenium, brainstem) with VMI and reading scores on WRAT-RE	Lower FA of the lateral splenium-parietal WM bilaterally associated with poorer VMI only within the FASD group
Correlation of FA and MD in 4 deep GM (thalamus, globus pallidus, putamen, and head of the caudate nucleus) and 10 WM (gCC, bCC, sCC, UF, SLF, ILF, CST, IFO, SFO, CNG) with cognitive deficits (working memory, quantitative concepts [mathematical ability], reading achievement and vocabulary proficiency, and some measures of executive functioning)	–
Comparing FA and MD of whole brain WM in FAS and non-FAS PAE	Lower FA only in bCC in FAS vs. non-FAS
Comparing FA, MD, AD and RD of whole brain WM in dysmorphic and nondysmorphic PAE and TD; correlation of DTI metrics with dysmorphia and IQ	Lower FA in iCC only in comparing dysmorphic to TD, a continuum of mean of DTI measures (FA, MD, RD) between three groups in sCC and iCC
Correlation of FA and MD in posterior mid-body of CC, sCC and iCC with dysmorphology; correlation of FA and MD in gCC and sCC with verbal comprehension, perceptual organization, working memory, and processing speed	Positive correlation of FA of gCC with working memory, inverse correlations between MD in sCC and the perceptual organization index score and working memory.
Correlation of FA, RD, and AD of whole brain VBA with quantitative concepts (math ability) in all FASD and in only right-handed FASD	Positively correlated with math ability in all FASD: FA in left anterior cerebellum cluster (MCP) and left parietal lobe (L-SLF, L-CST and bCC) and inverse correlation of FA in bilateral brainstem (ALIC, PLIC and cerebellar tracts); positive correlation with AD in left parietal and RD in two other clusters; in right-handed FASD: Positive correlation with FA in left cerebellar, left parietal and left splenium cluster and inverse correlation of FA in left occipital cluster
DMN activation in fMRI and FA, MD, RD, AD in cingulum comparing dysmorphic and nondysmorphic PAE	DMN deactivation: Dys < Nondys < TD, suggesting higher PAE with more attention disruption; lower FA and higher RD in cingulum in both PAE vs TD but higher MD only in dysmorphic PAE vs TD
Correlation of FA and RD in L-MCP with age, gender, IQ, FASD severity (FAS, pFAS), EBC	FA of L-MCP: FAS < pFAS<TD. RD of L-MCP: FAS > pFAS>RD; lower FA and higher RD in L-MCP related to dose of PAE. Trace conditioning (significant) and delay conditioning (trend) associated with higher FA and lower RD in L-MCP.
Correlation of functional connectivity in the para-central ROIs on CC with dysmorphology; correlation of interhemispheric connectivity of paracentral ROIs with FA and MD of iCC and post-midbody of CC; correlation of Para-central connectivity measure and MD in iCC and sCC with verbal comprehension, perceptual reasoning, working memory, and processing speed	Lower inter-hemispheric functional connectivity in cases and TD associated with higher MD in posterior mid-body of CC (and a trend in iCC); A trend in positive correlation between perceptual reasoning and inter-hemispheric connectivity and structural connectivity measures were stronger predictors than the functional connectivity measure.
Correlation of FA of L-ant corona radiata and R-external capsule with full-scale IQ, visuomotor integration and executive control (trail making test)	Across-group contribution of visuomotor integration performance toward predicting FA in R-external capsule
Correlation of longitudinal changes in FA, MD and volume in gCC, bCC, sCC, CST, ALIC, SFO, IFO, ILF, SLF, cingulum, UF with cognitive tests comparing more severe FASD with less severe FASD and TD.	Greater reductions of MD in SLF and SFO corresponded to larger gains in reading performance and greatest reductions in MD of SFO had the largest gains in reading performance and receptive vocabulary scores between scans only in FASD. More severe FASD had largest changes in MD of IFO and similar trend in SFO, UF and SLF than less severe FASD than controls.
Correlation of FA, MD, RD, AD with pro and antisaccade reaction time and direction errors	Correlation with SRT in **antisaccade task**: Positive correlation with FA and AD and negative correlation with RD in CC; **prosaccade task:** Positive correlation with AD in CC, FA in gCC, FA in R-ILF and neg correlation in FA and AD in L-cerebellum cluster (MCP in tractography), RD in gCC and RD in R-ILF
Correlation of FA and MD in 6 regions of CC with direction errors in antisaccade task and timing errors from the memory guided task	Direction errors: Negative correlation with FA in sCC and positive correlation with MD in sCC only in TD
Correlation of FA, MD, RD, AD in cerebellar peduncles with EBC; comparing DTI metrics among FASD severities (FAS, pFAS) and dosage of PAE	Higher FA in bilateral SCP associated with more optimal EBC performance at 5 years. Higher MD in L-MCP in FAS/pFAS associated with poorer EBC performance at 9–10 years; FA in bilateral SCP: FAS < pFAS<TD, only pFAS had higher MD in R-ICP vs. TD; greater alcohol consumption associated with lower FA and higher RD in SCP, with no relation between extent of alcohol exposure and AD. Greater AA/day associated with greater RD in L-MCP
Correlation of total brain volume, WM volume and WM fraction and FA, MD, AD, PD in 5 WM networks (CC+ corona radiata, R and L association and R and L projection fibers) with dosage/frequency of PAE, mother's cigarette smoking, maternal age at delivery, infant's age and sex	More frequent PAE associated with smaller intracranial volumes, greater PAE correlated with higher FA in R-association fibers and with lower MD and AD in all networks and strong association with lower AD in CST, superior and posterior thalamic radiations, UF, SLF, ILF. Older age at scan associated with lower MD in the R-projection network, lower AD in R-projection, B-association, and lower PD in R-association. Post conception age at scan associated with higher FA in the projection networks, particularly in the medial regions. Older maternal age associated with lower FA and higher MD in the R-association network and lower AD in L-projection and L-association. Girls with higher FA in the R-association network and lower AD in R-projection. Maternal smoking during pregnancy positively correlated with higher PD in all five networks, although these associations fall short of statistical significance

(*Continues*)

TABLE 1 (Continued)

Symptomatology correlations with DTI metrics	
Investigated cognitive domain, facial dysmorphology, FASD severity, or amount of PAE related to WM integrity	**Significant associations**
Correlation of FA, MD, RD, AD of SLF, SFOF, UF, cerebellar peduncles, CST, cerebral peduncle, posterior thalamic radiation, fornix, cingulum and CC with neonatal behavioral subscale of Dubowitz neurobehavioral scale including irritability, cry, consolability, alertness, visual and auditory orientation and eye movements	Scores on the behavioral subscale positively correlated with FA and negatively correlated with MD in R-ICP of alcohol-exposed infants.
–	–
Correlation of FA, MD, RD, AD in WM tracts, which differed between FASD and TD, with dosage of PAE, WISC-IV IQ (full scale and each of the four index scores), CVLT (short- and long-delay free recall), and EBC; comparing FAS/pFAS with nondysmorphic PAE and TD	Highest average values of alcohol exposure and lower IQ in the FAS/pFAS group than nondysmorphic PAE; FAS/pFAS vs. TD: Lower FA in R-ILF, sCC, iCC and higher MD in sCC, iCC, ILF, R-SLF, CST; Nondys vs. TD: Lower FA in L-ILF, sCC and higher MD in iCC, sCC, L-ILF, R-CST; all three continuous measures of PAE (AA/day, AA/occasion and days/week) significantly associated with lower FA in ILF, sCC, iCC and with higher MD in ILF, sCC, iCC, R-SLF, CST. After controlling for potential confounders AA/day remained significantly associated with FA in L-ILF, sCC, iCC and with MD in ILF, sCC, iCC. Increasing alcohol exposure associated with lower FA which was more attributable to higher RD rather than AD. Increased alcohol exposure associated with increased AD in B-ILF, sCC, iCC, and increased RD in L-ILF, iCC. Mean MD values in the peak ROIs positively associated with each of the 3 continuous measures of alcohol exposure; higher MD in L-ILF associated with poorer performance on all five IQ measures and to short-delay free recall on the CVLT. Higher MD in sCC and iCC associated with lower full-scale IQ, slower processing speed, and poorer EBC. Higher MD in sCC associated with poorer WISC-IV verbal comprehension and CVLT short-delay free recall; MD of R-SLF and CST related to cigarette.
Correlation between FA and MD of gCC, bCC, sCC, cingulum and UF with measures from the prosaccade task (saccadic reaction time, anticipatory saccades, amplitude, additional saccades, and saccade endpoint); correlation between FA and MD of gCC, bCC, sCC, cingulum, UF, ILF, SLF, IFO, CST with animal sorting, auditory attention, response set, inhibition, arrows, digit recall, and block recall standard scores; age and sex interactions were assessed.	TD females had higher FA in gCC, L.SLF and L. UF than PAE females. Males had higher FA in L.CST than females. TD males had lower FA in R.ILF than TD females; FA increased with age for the majority of the tracts in both groups, 73% (11/15 tracts) in controls and 93% (14/15 tracts) in PAE. The same proportions of tracts showed reductions of MD with age; positive correlation between MD of bCC and additional saccades in TD and MD of L-cingulum and additional saccades in PAE. Negative correlation between FA of gCC (trend in bCC) with additional saccades in TD. Negative correlation between FA of R-UF and saccade endpoint angle of error in TD.
Correlation of FA and MD of gCC, bCC, sCC, ILF, SLF, cingulum, UF, CST, IFO, SFO with several cognitive tests; age and sex interactions were assessed.	A significant main effect of age on FA (increasing) from 5 to 32 for bCC, sCC, CST, IFOF, cingulum and UF, similar in both groups, but steeper increases of FA with age for SLF and ILF in TD, and for gCC in FASD. MD decreased significantly with age in all tracts, with similar slopes in both groups. No significant effects of sex or sex-by-group interactions for MD of any tract. A significant effect of sex for FA of gCC, bCC, CST and cingulum which males had higher FA than females in both groups. A significant sex-by-group interaction for FA of SLF, indicating group differences greater among males (2.5% higher in control than FASD) than in females (1.5% higher in control than FASD); positive correlation between hippocampal volume and visuospatial memory only among female FASD. A positive correlation between FA of gCC, SLF, ILF and reading ability only among females with FASD, but not among female controls or males in either group. Positive correlations between executive functioning and IQ scores with caudate, thalamus, and Globus pallidus volumes only in female FASD. No sex differences of cognitive deficits in this FASD sample
Correlation of FA and MD of cingulum, CST, IFO, SFO, optic radiation, SLF, UF, fornix, bCC with age and gonadal hormones (T, P, E2, DHEA, T:DHEA ratio) separately among boys and girls (T = testosterone; P = progesterone; E2 = ethinyl estradiol)	**Boys**: Significant group-age interactions for gCC and optic radiation, where a positive association between FA and age in TD but not PAE. Positive association between FA and T levels in TD, but not in PAE. Positive association between FA of IFO and T levels in TD and a trend for a negative association in PAE. Negative association between FA of SFO and T levels in PAE, but not in TD. Positive association between FA of SFO and DHEA levels in TD, but a negative association in PAE; **girls:** Positive association between FA of SLF and T levels in PAE but not in TD. Positive association between FA of CST and SLF with DHEA levels in PAE, but not in TD. a trend for a positive association between FA of SLF and T:DHEA ratios in TD, but a significant negative association in PAE. Negative association between FA of fornix and P in TD and not PAE.

Complementary information of participants				
Cases and TD matched in:	**Cases and TD differed in:**	**Exposure to other drugs in utero, psychiatric comorbidities, psychoactive medication**	**Alcohol consumption during pregnancy in cases**	**Alcohol consumption during pregnancy in TD**
Age, gender, ethnicity, SES	FSIQ, processing speed	–	At least two drinks per week; ounces of absolute alcohol exposure during pregnancy for each participant reported	0 oz of absolute alcohol exposure
Age, gender, birth weight and length, current weight, and height	IQ	Exposure to other drugs except tobacco excluded; major psychiatric disorders excluded	High exposure in 11 of 14 cases (Astley and Clarren rating 54). Alcohol use heavy, extensive, involved frequent intoxication, and often persisted throughout pregnancy. Alcohol exposure confirmed for the remaining 3 cases, but the level lower or not specified (Astley and Clarren rating 53). About 3 to 4 beers per day, 3 or 4 times per week until the mother became aware of pregnancy in one case. In another case, the adoptive parents had observed the biological mother using alcohol to intoxication during pregnancy but could not specify her frequency of use.	Excluded if even minimal alcohol consumption was reported any time during pregnancy

TABLE 1 (Continued)

Complementary information of participants				
Cases and TD matched in:	**Cases and TD differed in:**	**Exposure to other drugs in utero, psychiatric comorbidities, psychoactive medication**	**Alcohol consumption during pregnancy in cases**	**Alcohol consumption during pregnancy in TD**
Age, gender, handedness, maternal education	IQ, ethnicity (lower number of Caucasians in FASD)	Some of the children were exposed to other drugs in utero (e.g., marijuana, tobacco)	Not specified	Not specified
Not assessed	Not assessed	–	Information not available	Not exposed?
Age, sex, race, SES	IQ	–	A minimum of 4 drinks per occasion at least once per week or 14 drinks per week during pregnancy.	Not exposed?
Age, sex, SES, ethnicity, age, education, IQ, cocaine and cigarette during pregnancy, height	Marijuana during pregnancy, adult head circumference, brain weight	–	Ounces of absolute alcohol exposure during pregnancy reported. At least two drinks per week.	Not exposed
Age, gender,	Cognitive functioning such as IQ	Other prenatal drug exposure except nicotine and caffeine excluded	Astley and Clarren rating of alcohol exposure for each case. Not heavy exposure excluded based on Astley and Clarren ratings	Not exposed
No control	No control	Exposure to other drugs in utero, including tobacco, marijuana, and cocaine reported for 13 subjects	Specific information about quantity and timing of alcohol use during pregnancy not available for most subjects; significant alcohol exposure confirmed in all cases.	No control
Age, ethnicity, monthly income, education, prenatal marijuana exposure	Gender, IQ (Dys < TD), current alcohol use by participant (Dys > non-dys, TD), prenatal cigarette and cocaine exposure	–	Mean ounces of absolute alcohol consumption per week. 1–2 drinks/week	0 oz of absolute alcohol exposure
Maternal age, education, marital status, or parity or child gender, age, or grade in school	IQ, gestational exposure to cigarette, weight, head circumference,	Lead exposure	Heavily exposed: At least 14 standard drinks per week (1.0 oz AA/day) on average or engaged in binge drinking (4 or more drinks/occasion). Levels of PAE averaging 6.5 drinks/occasion for FAS	Minimally exposed, levels of PAE averaging 0.17 drinks/occasion for FAS
Age, gender, handedness, maternal education	Nothing reported	Other prenatal drug exposure except nicotine, caffeine, cocaine, marijuana excluded; psychiatric comorbidities in FASD: ADHD (76%); ODD (29%); PTSD (24%); disruptive behavior disorder not otherwise specified (24%); reactive attachment disorder (10%); developmental communication disorder (10%); MDD (5%); anxiety disorder not otherwise specified (5%).	Astley & Clarren ratings, excluded if minimal consumption	Not exposed
Age, sex, handedness, parental education, parental IQ, family income	IQ score, VMI score, birth weight, adoption rate, nicotine exposure rate	Psychiatric comorbidities: ADHD, BPD, major depression, OCD	≥4 drinks on any occasion or ≥14 drinks in any week	Not exposed
Age at first and last scans, sex, SES	Ethnicity, handedness, caregiver status (FASD most adopted), psychiatric comorbidities (only in FASD), psychoactive medication (only in FASD)	Psychiatric comorbidities in FASD: 11 ADHD, 4 anxiety, 5 ODD and 6 other;psychoactive medication: 11 atypical antipsychotic, 10 psycho-stimulant, 5 antidepressant, 3 other	Not specified	14 no, 2 unknown, 5 minimally exposed (range: 1–3 drinks; average of two drinks total during pregnancy)
No control	No control	Psychiatric comorbidities: 6 ADHD, 3 anxiety, 3 depression, 4 ODD, 1 bipolar mood disorder, 1 reactive attachment disorder	Not specified	No control
Age, sex, handedness, SES	Ethnicity, comorbidities only in FASD, medications only in FASD	Psychiatric comorbidities: 25 ADHD, 5 ODD, 7 anxiety, 4 depression, 16 other; Medications: 22 stimulants, 11 antipsychotics, 5 antidepressant, 2 other	Not specified	Not specified

(*Continues*)

TABLE 1 (Continued)

Complementary information of participants				
Cases and TD matched in:	**Cases and TD differed in:**	**Exposure to other drugs in utero, psychiatric comorbidities, psychoactive medication**	**Alcohol consumption during pregnancy in cases**	**Alcohol consumption during pregnancy in TD**
Sex, lead exposure, gestational exposure to cigarette	Age, IQ, maternal age at delivery, maternal education, SES	Exposure to cocaine (1pFAS), marijuana (1 FAS, 2 PFAS, 1 heavily exposed, and 1 TD) exclusion and inclusion of these participants did not cause difference in output results.	Heavy drinkers who consumed 14 or more standard drinks/week (1.0 oz AA/day) and/or engaged in binge drinking (5 or more drinks/occasion); levels of PAE averaging 10.0 drinks/occasion for FAS, 7.2 for PFAS and 6.8 for the nonsyndromal	Abstained from drinking or drank no more than minimally during pregnancy
Birthweight, age at birth, post conception age at scan, maternal education, parity, smoking, marijuana	Head circumference, sex, maternal age at delivery (older in PAE)	Other drugs such as cocaine and methamphetamine excluded; marijuana used (in small quantities) by mothers of one PAE and two TD infants; average number of cigarettes smoked per day during pregnancy reported	Heavy drinkers, who consumed 14.0 or more standard drinks/week (1.0 oz AA/day) and/or engaged in binge drinking (4 or more drinks/occasion	All abstained but one drank two drinks per occasion about twice per month
Gestational weeks, age, maternal smoking, sex, weight, head circumference, length	Behavior	Newborns of the mothers with a positive urine screen for other drugs of abuse (any group) excluded; smoking in 13 PAE and 19 TD	Moderate–severe alcohol use (either drinking two or more times a week or two or more drinks per occasion; exact doses of alcohol separated by 3 trimesters are reported	Not specified
Age, sex	SES, IQ	Drugs and comorbidities: 9 ARND had comorbidity of ADHD with or without other comorbidities such as learning disability, conduct disorder, global delay, ODD, depression, and attachment disorder.	Not specified	Not specified
Maternal age at delivery, age and sex, cigarettes smoked during pregnancy	Maternal education (lower in FASD), lead exposure (higher in FAS, pFAS), IQ (lower in FAS/pFAS) higher doses of PAE (FAS/pFAS)	Cigarettes smoked per day and lead exposure reported; 3 women reported using marijuana (1–3 days/month), one used cocaine, and none used methaqualone ("mandrax"): After omitting these participants output findings remained unchanged.	Minimum of 14 drinks per week (1.0 oz AA/day) or at least two incidents of binge drinking (5 drinks per occasion) during the first trimester of pregnancy	Abstained from drinking and one consumed 2 drinks on 3 occasions
Age, sex, SES	Ethnicity, comorbidities only in FASD, medications only in FASD	Psychiatric comorbidities: 37 ADHD, 5 ODD, 9 anxiety, 6 depression, 24 other), medications: 28 stimulants, 11 antipsychotics, 5 antidepressant, 2 other	Not specified	Not specified
Age, sex	Ethnicity,living situation, annual household income, comorbidities and psychiatricmedication use (2controls and 26fasd missing)	TD: 12 were prenatally exposed to nicotine (all via cigarettes in varying frequencies and amounts) and none were prenatally exposed to illicit drugs; 3 TD had anxiety. FASD: 38 ADHD, 10 reactive attachment disorder, 13 anxiety, 19 other; medications: 24 atypical antipsychotics, 20 stimulants, 11 antidepressants, 9 other.	Not specified	Exposure to>2 drinks per occasion or >6 drinks in total excluded. Seven TD were prenatally exposed to alcohol within the threshold for inclusion (average exposure: 3 drinks total)
Age, sex, site, time of saliva collection	Nothing reported	–	Moderate to severe levels of alcohol (≥13 drinks/week or >4 drinks/occasion	Excluded if exposed to >1 drink per week on average or >2 drinks on a single occasion

Higher FA or lower MD in cases versus TD are written in bold.

CC, corpus callosum; gCC, bCC, sCC, iCC, genu, body, splenium, isthmus of corpus callosum; SFO, IFO, superior and inferior fronto-occipital fasciculi; SLF, ILF, superior and inferior longitudinal fasciculi; CST, corticospinal tract; UF, uncinate fasciculus; SCP, MCP, ICP, superior, middle, inferior cerebellar peduncles; R-, right; L-, left; WM, white matter; GM, gray matter; FASD, fetal alcohol spectrum disorder; FAS, fetal alcohol syndrome; pFAS, partial FAS; ARND, Alcohol-Related Neurodevelopmental Disorder; PAE, prenatal alcohol exposure; TD, typically developed; (Non)Dys, (non-)dysmorphic; MR, mental retard, SES, socioeconomic status; EBC, eyeblink conditioning; VMI, visuomotor integration.

[a] Numbers present whom DTI data were analyzed.

[b] Since number of males/females in the studies are representative of all cases included and not only cases with DTI measures, this number in some studies is not apparent.

(Table 2). Most of the studies have represented the pattern of alcohol consumption during pregnancy. Some of the studies have also reported the exact dose and frequency of maternal alcohol consumption. TD groups are generally non-exposed, and a few ones are minimally exposed individuals, while cases are heavily exposed or are diagnosed with FASD. Most of the studies have relied on the Astley and Clarren 4-digit diagnostic system to diagnose FASD (Astley, 2004). Comorbidities, medications, or abuse of alcohol or other drugs by individuals with PAE are among the reported confounding environmental factors, which may interfere with observed neural changes caused by alcohol teratogenesis. Only eight studies report psychiatric comorbidities such as attention deficit hyperactivity disorder (ADHD), depression, or anxiety disorders to some extent (Table 1). In addition, in-utero exposure to other drugs such as nicotine, caffeine, cocaine, marijuana, and methamphetamine are reported or used as an exclusion criterion in less than half of the studies. Two studies have been conducted on PAE in the neonatal period, and participants in other studies are not younger than 5 or not older than 32 years old. PAE and TD are age-matched and gender-matched in almost all studies. However, cognitive function and IQ are consistently lower among PAE.

4 | DTI FINDINGS IN FETAL ALCOHOL SPECTRUM DISORDERS

Of all the reviewed articles, 6 have focused only on the corpus callosum (CC), 2 on cerebellar peduncles, and 1 study on the cingulum bundle as regions of interest. Other studies have surveyed almost all the major white matter tracts. Overall, studies have found altered integrity in association fibers (such as inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFO), superior fronto-occipital fasciculus (SFO), uncinate fasciculus (UF), and arcuate fasciculus), projection fibers (such as cerebrospinal tract [CST]), callosal tracts, as well as fewer reports about brainstem and subcortical gray matter structures. Studies conducted on children, adolescents and adults have mostly revealed reduced FA and/or increased MD and/or increased RD in widespread regions of WM. However, two studies in the neonatal period have emphasized on the reduced AD in FASD compared with TD newborns. Furthermore, two studies have not found any significant neural differences between 19 FASD and 27 TD with a mean age of about 10 years old (Colby et al., 2012), or between 70 FASD and 74 TD between ages 5 and 32 years old (Treit et al., 2017). In addition, there are few reports of higher FA (in structures such as globus pallidus; Lebel, Rasmussen, et al., 2008), right cingulum and right posterior limb of the internal capsule; Fryer et al., 2009) or lower MD (in genu; Lebel, Rasmussen, et al., 2008, right anterior corona radiata and right forceps major; Fryer et al., 2009) comparing PAE with TD; or in relation to cognitive tasks, such as higher FA in bilateral brainstem cluster containing anterior and posterior limbs of the internal capsule in association with decreased math ability (Lebel et al., 2010), and higher FA in right CC and right ILF correlated with higher prosaccade and antisaccade reaction times (Green et al., 2013). There are also some discrepancies regarding the left, right or bilateral involvement of major white matter tracts among studies. Left dominant alterations are observed in temporo-parietal white matter, and long association fibers in the cohorts of Lebel et al. (Lebel et al., 2010; Lebel, Rasmussen, et al., 2008) and Paolozza et al. (2017), respectively. However, bilateral or right-sided alterations are also frequently reported by other studies. Atypical lateralization in several neurodevelopmental disorders has been linked to cognitive abilities, primarily in the language domain (Moncrieff, 2010). However, despite some evidence of the differential effect of ethanol on each hemisphere, no DTI assessment has been conducted to compare anisotropic indices between left and right hemispheres in FASD. It is noted that nonright handedness is much more prevalent in patients with FASD compared with TD. Even right-handed individuals with FASD tend to have weak hand preference, suggesting reduced lateralization (Domellöf, Rönnqvist, Titran, Esseily, & Fagard, 2009). Cortical asymmetry in children with FASD is shown in the study by Sowell et al. (2002) by means of increased volume in the right orbitofrontal area, implicated in response inhibition, and in the left temporoparietal gray matter (Sowell et al., 2007), involved in language processing. They also showed that increased cortical thickness in the right dorsal prefrontal region was associated with better verbal abilities in children with PAE (Sowell et al., 2007). Since cortex thins during normal pruning and myelination (Toga, Thompson, & Sowell, 2006), this counterintuitive result is perhaps indicative of compensatory changes in response to left temporoparietal disturbance. Potential compensatory changes were also seen in an fMRI-DTI study comparing individuals with the alcohol-related neurodevelopmental disorder (ARND) with TD subjects (O'Conaill et al., 2015). This study showed that subjects with ARND use dorsal attention pathway (activated normally for effortful tasks) for automatic visual search tasks instead of the ventral pathway, which is compromised due to ILF disruptions. Further investigation of the effect of PAE on brain laterality is obviously needed to shed light on the present complex picture of findings by DTI studies.

5 | CORPUS CALLOSUM

The corpus callosum (CC), structurally and functionally prominent in the brain, is the largest commissural tract that actively connects the two cerebral hemispheres. Developing relatively early between 10th and 20th gestational weeks (Adam, 2016), CC keeps growing until the third decade of life (Riley et al., 1995). The callosal formation starts from genu, followed by the body, splenium, and lastly the rostrum. This is while myelination progresses relatively slow in a posterior to anterior direction (Hellige, 1993; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). The first autopsies of prenatally alcohol-exposed brains, particularly in dysmorphic individuals, have reported complete (Jones & Smith, 1973; Pfeiffer, Majewski, Fischbach, Bierich, & Volk, 1979; Wisniewski, Dambska, Sher, & Qazi, 1983) or partial agenesis of the corpus callosum (Kinney, Faix, & Brazy, 1980) or an extremely thinned CC (Clarren, Alvord, Sumi, Streissguth, & Smith, 1978; Coulter, Leech, Schaefer, Scheithauer, & Brumback, 1993). Since then the sensitivity of corpus callosum to alcohol teratogenesis has been highlighted in FASD, though to a far lesser extent in most individuals. A variety of CC alterations have been revealed in magnetic resonance

imaging of individuals with FASD, ranging from complete agenesis to less severe alterations such as hypoplasia and marked thinning, more frequently localized in posterior regions of CC (McGee & Riley, 2006; Roebuck, Mattson, & Riley, 1998). Despite these gross anomalies, quantitative studies have reported disproportionate volume reductions in sub-regions of CC such as genu and splenium after accounting for total brain sizes in PAE (Autti-Rämö et al., 2002; Riley et al., 1995). In addition to the reduced callosal area, more prominently in the splenium, Sowell et al. revealed dislocated posterior section of CC (isthmus and splenium) in FASD, with a significant correlation between the amount of dislocation with facial dysmorphology and with impaired verbal learning (Sowell et al., 2001). Greater variability of callosal shape, especially in the isthmus and splenium, has also been documented in PAE from infancy to adulthood, and that thicker or thinner structure is linked to executive dysfunction and motor impairment, respectively (Bookstein et al., 2007; Bookstein, Sampson, Connor, & Streissguth, 2002; Bookstein, Streissguth, Sampson, Connor, & Barr, 2002). Regardless of the consistent implication of CC alterations in FASD, no specific macrostructural pattern is demonstrated among different cohorts. In addition, many studies have failed to observe macrostructural anomalies among all subjects. As a result, evaluation of CC in microstate domains deemed necessary. Furthermore, a multimodal imaging study on individuals with PAE has revealed a few correlations between different structural domains such as volumetric measures and white matter integrity (Treit et al., 2017).

5.1 | Between-group differences of DTI parameters in the corpus callosum

The corpus callosum is by far the most studied white matter structure, including by DTI studies. As detailed in Table 3, group comparisons of CC microstructural integrity in alcohol-affected individuals versus nonexposed or minimally exposed groups have revealed diffusion parameter alterations across the entire CC, but more consistently in posterior regions. These abnormalities appear across the range of FASD diagnoses and from childhood to young adulthood. Findings from DTI studies agree with aforementioned morphological surveys regarding variable effects of alcohol insult on CC. In fact, sub-regions of CC vary in terms of histology and cortical projections (Huang et al., 2005). Although there is no definite anatomical landmark within CC, thin fibers are densest in the genu and mid-splenium, interconnecting high-order processing prefrontal and temporoparietal cortices. This is while largest fibers are mostly located in the midbody to bridge between primary and secondary sensory and motor areas (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). Variation along the CC (Wozniak et al., 2006) may reflect dissimilar regional susceptibility of CC. In other words, the grandstanding of splenium/isthmus may signify the more defenselessness of neural structure in these regions to the teratogenicity of ethanol.

As shown in Table 3, most often lower FA or higher MD is accompanied by higher RD, which may suggest damage to the myelination or axonal packing as the main underlying pathogenesis (Song et al., 2005). Oligodendrocytes, which produce the myelin sheath for central axons, die before any other types of glial cells in the presence of ethanol (Benjamins, Nedelkoska, Lisak, Hannigan, & Sokol, 2011). Animal studies have revealed the susceptibility of glial cells and in particular the oligodendrocytes, to the prenatal alcohol exposure (Guerri, Pascual, & Renau-Piqueras, 2001; Ozer, Sarioglu, & Güre, 2000; Phillips & Krueger, 1992). This is of particular interest that mediation of alterations by RD are reported in studies that have examined individuals more than 5 years old. Tylor et al. have studied DTI metrics in newborns of alcoholic mothers with reported moderate to heavy alcohol consumption and no use of other drugs. They demonstrated that all white matter structures, including CC, had lower AD and MD values, with a dose-dependent response (Taylor et al., 2015). The reduced AD is replicated in another study of newborns in the right SLF, although they did not see any DTI metric changes in CC (Donald et al., 2015). These lines of evidence of AD alterations on white matter in newborns may postulate the axonal damage rather than myelin disruption through alcohol teratogenesis. On the assumption that alcohol teratogenesis is caused by multiple mechanisms (Goodlett, Horn, & Zhou, 2005), this question arises whether or not the effect of alcohol exposure during the prenatal period continues throughout the lifespan. In other words, is the probable myelin disruption, which is indirectly reported only in more mature stages of white matter, that is, ages 5 years old and above, a dynamic effect of a neurotoxin which is not present anymore? Evidence has deepened the effect of alcohol from the level of axons to the role of epigenetic mechanism in the development of FASD (for a detailed review please refer to Ungerer, Knezovich, & Ramsay, 2013]).

5.2 | Relationships between facial dysmorphology and callosal integrity

Although there are several reports of no association between loss of integrity in CC and facial dysmorphology (Ma et al., 2005; Wozniak et al., 2006; Wozniak et al., 2009; Wozniak et al., 2011), Fryer et al. showed that among major white matter involved in FASD, only reduced FA in the midbody of the CC can distinguish 6 dysmorphic from 6 nondysmorphic individuals with FASD (Fryer et al., 2009). This relationship was better illustrated by a voxel-based analysis (VBA) method, confirming a continuum of lower FA and higher MD and RD of the isthmus, where parameters in nondysmorphic FASD fell between those of dysmorphic and nonexposed healthy controls (Li et al., 2009). It is also demonstrated that there is a continuous decrease in callosal volume, progressing across the more severe form of FASD with facial dysmorphology to less affected children (Astley et al., 2009). A recent longitudinal DTI study on a cohort of South African patients with known exact doses of alcohol consumption during pregnancy has revealed that teratogenic damage to the splenium and isthmus is dose-dependent (Fan et al., 2016). The pattern of alcohol consumption during pregnancy, including the amount, frequency, and temporal window of exposure affects the process of maldevelopment (Cudd, 2005; Goodlett et al., 2005; O'Leary-Moore, Parnell, Lipinski, & Sulik, 2011). Since higher doses of alcohol presented to the developing embryo may relate to more severe physical and behavioral alterations, it can be proposed that DTI measures in CC as a midline structure may reflect the extent of alcohol exposure and severity of the damage. Correlation of higher degrees of facial dysmorphology with greater amounts of alcohol exposure in utero and lower intellectual performance was verified in a large sample of FASD with overall and regional brain volume reductions (Roussotte

TABLE 2 Quality assessment of reviewed case–control studies

Study	Quality indications of Newcastle–Ottawa scale								Total
	A	B	C	D	E	F	G	H	
Ma et al., 2005	1	1	1	0	1	1	1	1	7
Wozniak et al., 2006	1	1	1	1	1	1	1	1	8
Sowell et al., 2008	1	1	1	1	1	1	1	1	8
Lebel, Rasmussen, et al., 2008	1	1	1	1	1	1	1	1	8
Fryer et al., 2009	1	0	1	1	1	1	1	1	7
Li et al., 2009	1	1	1	1	1	1	1	1	8
Wozniak et al., 2009	1	1	1	1	1	1	1	1	8
Lebel et al., 2010	Case series study								
Santhanam et al., 2011	1	1	1	0	1	1	1	1	7
Spottiswoode et al., 2011	1	1	1	0	1	1	1	1	7
Wozniak et al., 2011	1	1	1	1	1	1	1	1	8
Colby et al., 2012	1	1	1	0	1	1	1	1	7
Treit et al., 2013	Longitudinal study								
Green et al., 2013	Case series study								
Paolozza, Rasmussen, et al., 2014a, Paolozza, Rasmussen, et al., 2014b	1	1	1	1	1	1	1	1	8
Fan et al., 2016	1	1	1	0	1	1	1	1	7
Taylor et al., 2015	1	1	0	0	1	1	1	1	6
Donald et al., 2015	1	1	1	0	1	1	1	1	7
O'Conaill et al., 2015	1	0	1	1	1	1	1	1	7
Fan et al., 2016	1	1	0	0	1	1	1	1	6
Paolozza et al., 2017	1	1	1	0	1	1	1	1	7
Treit et al., 2017	1	1	0	1	1	1	1	1	7
Uban et al., 2017	1	1	0	0	1	1	1	1	6

A. Adequate definition of case; B. Representativeness of Cases; C. Selection of controls; D. Definition of controls; E. Control for important factor or additional factor; F. Exposure Assessment; G. Same method of ascertainment for cases and controls; H. Nonresponse rate.

et al., 2012). The relationship between facial dysmorphology and brain damage is echoed in a volumetric study showing greater thickness in cortical measures correlated with more severe midfacial dysmorphology (Yang et al., 2011). On the other hand, two studies by Bookstein et al. did not find any significant relationship between facial dysmorphology and callosal macroscopic measures (Bookstein et al., 2007; Bookstein, Streissguth, et al., 2002).

Studies in animal models have shown that alcohol exposure at very early stages of prenatal development will result in craniofacial abnormalities consistent with those in human FAS. However, later times of exposure produce different patterns of brain and facial anomalies. Sharing the same progenitor cells, the development of midline facial and cranial structures are proposed to be compromised by cell damage from alcohol exposure (O'Leary-Moore et al., 2011; Sulik, 2005). It should be noted that the relationship between facial dysmorphology and brain structure may be more apparent during childhood, as facial dysmorphology attenuates in adolescence (Lemoine, 1992). Larger samples of children are required to clarify the relationship between brain structure and facial dysmorphology in humans.

5.3 | Cognitive performance and callosal integrity

Several domains of executive function such as working memory, response inhibition, and visuomotor integration are impaired in individuals with FASD (Mukherjee, Hollins, & Turk, 2006). Saccades and antisaccades in eye movement control involve higher level inputs and thus have become important measures to probe discrete cognitive functions such as goal-directed behavior, response inhibition, visuospatial skills, and working memory simultaneously (Leigh & Zee, 2015; Paolozza, Rasmussen, et al., 2014a; Paolozza, Rasmussen, et al., 2014b). The posterior parietal cortex serves as the crossing point between sensory and motor pathways in the eye movement control circuitry. This area projects to the oculomotor primary and supplementary frontal areas and dorsolateral prefrontal cortex which have a key role in decision making, executive function, spatial working memory and suppressing involuntary, reflexive responses (Leigh & Zee, 2015). Coordinated movement of the eyes demands the active transfer of visual information between two hemispheres (Leigh & Zee, 2015). Fibers from the frontal lobe project through the genu and a large part of the anterior body of the CC, while parietal fibers project through a wide portion of the posterior body of the CC as well as the posterior–superior portion of the splenium to reach to the homologous parts in the opposite hemisphere (Huang et al., 2005). Although little is known about white matter contribution to the eye movement, it is expected that CC is crucial to have an executive and flexible control of eye movements.

Correlations of DTI parameters in the CC with eye movement control deficits in individuals with FASD have led to intriguing results. Paolozza, Treit, Beaulieu, & Reynolds, 2014 showed that FASD individuals (7–18 years old) with higher MD values in the splenium perform worse in response inhibition, reaction time, and spatial working

memory than TD. However, FA and MD were related to direction errors in the antisaccade task, a measure of response inhibition, only in healthy controls, and not in individuals with FASD. In this study, they just focused on CC by manual deterministic tractography. Later, the authors adopted a semi-automated tractography on added major white matter tracts and displayed lower FA and higher MD values in genu and splenium in relation to increased additional saccades only in typically developing children. Again, damaged CC in a cohort of individuals with FASD (5–18 years old) did not show any correlations with behavioral errors. The same behavioral measure was instead associated with higher MD in left cingulum in PAE. As cingulum is involved in higher cognitive controlling of eye movement (Leigh & Zee, 2015), the authors suggest that higher order regions of the FASD brain may be engaged in more automatic behaviors such as saccade and prosaccade tasks (Paolozza et al., 2017).

On the other hand, Green et al., 2013 have illustrated the inverse relation between FA in the cerebellum (an important structure in executing fast, accurate, and consistent eye movements) and prosaccade reaction time, whereas an unexpected increase in callosal FA was associated with the slower reaction in antisaccade and prosaccade tasks. Higher FA, although generally considered to reflect more organized tracts, can also result from lower axonal branching or reduced axonal diameter conjugated with increased membrane density and thus poor cognitive performance. However, this study used a relatively small sample size of 14 children with PAE (8–13 years old) and no controls. So, we do not know if there was a damage to the CC or not. These results may also point toward a compensatory role of interhemispheric connectivity in this set of tasks. Recovery or improvement of oculomotor deficits several weeks or months after acute damage to the oculomotor cortex is documented in monkeys or postStoke humans (Müri & Nyffeler, 2008). Clinical and transcranial magnetic stimulation studies have exhibited that this is the contralateral homologous cortex that pays for the shortage (Nyffeler, Müri, Pflugshaupt, Wartburg, & Hess, 2006; Sharpe, Bondar, & Fletcher, 1985).

Some other studies have tried to investigate the association of a battery of neurobehavioral tests in FASD with DTI parameters. Visual–motor integration (Sowell et al., 2008), visual–perceptual skills (Wozniak et al., 2009; Wozniak et al., 2011), eye blink conditioning, memory recall, intelligence, and processing speed (Fan et al., 2016) have been linked to microstructural and functional abnormalities in the most posterior CC. Lower FA in the genu and higher MD in splenium are shown to be related to the deficits of working memory (Wozniak et al., 2009). These deficits can contribute to poor academic performance, especially math abilities. Lebel et al. did not find any association between various cognitive aspects such as working memory, quantitative concepts, vocabulary or executive performance, and DTI parameters of the whole brain (Lebel, Rasmussen, et al., 2008). Yet in a subsequent study of the same cohort (Lebel et al., 2010), they showed math ability is positively related to FA and parallel diffusivity in the left parietal cluster, where the body of CC is one of the tracts passing through. Left splenial FA was additionally correlated to math ability in only right-handed FASD. While parallel diffusivity leads us to axonal damage as a probable cause of differed diffusivity, the study also showed likely demyelinated cerebellar cluster in terms of negative association of perpendicular diffusivity with math ability. This is a captured image of the complex effect of alcohol teratogenicity on neural cells. At the same time, some studies that have just explored CC have not found any association between CC and cognitive deficits such as intelligence (Li et al., 2009; Ma et al., 2005), verbal learning (Sowell et al., 2008; Wozniak et al., 2009) and processing speed (Wozniak et al., 2009). Successful cognitive performance demands a healthy multi-network structure and the scenario of "one single tract"–"one specific cognitive deficit" (Lebel et al., 2008) is not consistent with this fact. However, these findings bring evidence on the clinical relevance of CC alterations in FASD.

6 | CEREBELLAR PEDUNCLES

Morphological imaging has revealed reduced cerebellar volume in children and adolescents with a history of PAE (Astley et al., 2009; Autti-Rämö et al., 2002; Mattson et al., 1996; Sowell et al., 1996; West, 1993). Cerebellar hypoplasia is supported by animal studies in PAE (Maier, Miller, Blackwell, & West, 1999; Maier & West, 2001; Napper & West, 1995), which also claims that alcohol exposure early in pregnancy results in more neuronal loss (Goodlett, Marcussen, & West, 1990; Hamre & West, 1993; Thomas, Goodlett, & West, 1998). Moreover, as shown by Fan et al. (2016), there is a strong dose-dependent FA reduction in bilateral superior cerebellar peduncles and MD increase in the left middle cerebellar peduncle (MCP) in FASD. These alterations were also correlated with poor performance in eyeblink conditioning paradigm, a potential biomarker in individuals with PAE. They showed that higher doses of prenatal alcohol exposure cause higher RD scores in cerebellar peduncles. This result indirectly underscores the disruptive effect of ethanol mostly on the myelination. This finding is supported by another study by Spottiswoode et al. (2011). The authors showed that full FAS patients have the highest deficits in the left MCP in terms of lower FA and higher RD, and in correlation with eyeblink conditioning performance. Same parameters, FA and RD are also shown by Lebel et al. (2010) in relation with math ability in the bilateral MCP. Reduced FA, but this time with a lower AD of left MCP is shown by another study to mediate increased prosaccade reaction time in children with FASD (Green et al., 2013). The consistent reports of left MCP in these studies can be explained by the laterality of cognitive modulation in the cerebellum. In fact, it is well described that left cerebellum integrates right hemispheric cognitive functions including attentional and visuospatial skills (Baillieux et al., 2010). Therefore, it can be assumed that inputs from the right cortex to the cerebellum are interrupted by the damage to the left MCP in individuals with FASD and may affect performance in related cognitive tasks. Involvement of the inferior cerebellar peduncle is manifested in a study of neonates with FASD. This study has demonstrated that only lower FA and higher MD values of this tract are correlated with neonatal neurobehavioral tests. Although increased AD in SLF was the only difference observed between PAE and normal neonates. Even though the cerebellum is one of the most affected regions by prenatal alcohol exposure, few DTI studies have investigated this structure and only among individuals no more than 13 years old. Undoubtedly, more studies are needed to clarify the role of the cerebellum in cognitive manifestations of FASD.

TABLE 3 Altered integrity in the corpus callosum comparing PAE versus TD

Study	Age range in years (cases)	DTI analysis method	ROI on	FA reductions	MD increases	RD increases	AD increases
Ma et al., 2005	18–22	Manually defined tractography	Genu/ splenium	Genu/splenium	Genu, splenium		
Wozniak et al., 2006	10–13	Manually defined tractography	CC		Isthmus		
Sowell et al., 2008	7–15	VBA	7 regions (+CC)	Lat.Splenium			
Lebel, Rasmussen, et al., 2008	5–13	Semiautomated tractography (10wm)	Deep gray matter	Splenium	Genu ↓	Splenium	
Fryer et al., 2009	8–18	Voxel wise TBSS	CC	Body, forceps major	R-forceps major ↓		
Li et al., 2009	19–27	Voxel wise TBSS	CC	Isthmus (trend splenium and genu)	Isthmus	Isthmus	
Wozniak et al., 2009	10–17	Manually defined tractography	CC	Posterior midbody, splenium, isthmus (trend genu)			
Wozniak et al., 2011	10–17	Manually defined tractography	CC		Posterior midbody (trend in isthmus)		
Treit et al., 2013	5–15	Semiautomated tractography (11wm)			Genu		
Paolozza, Rasmussen, et al., 2014a, Paolozza, Rasmussen, et al., 2014b	7–18	Tract-specific	CC	Splenium	Splenium		Splenium
Taylor et al., 2015	36–44 weeks	Probabilistic tractography	Major WM (+CC)		CC ↓		CC ↓
Donald et al., 2015	2–4 weeks	TBSS	Major WM (+CC)	Nothing			
O'Conaill et al., 2015	10–14	TBSS			CC		
Fan et al., 2016	Longitudinal	VBA	Major WM (+CC)	Splenium, isthmus	Splenium, isthmus	Splenium, isthmus	
Paolozza et al., 2017	5–18	Semiautomated tractography	15 major WM (+CC)	Genu, body, splenium	Body		

7 | CINGULUM

Santhanam et al. (2011) have revealed reduced resting-state functional activity and decreased structural integrity in the cingulum. This bundle connects the medial prefrontal cortex and posterior cingulate gyrus, two nodes of default mode network. Therefore, cingulum is involved in attentional modulation during cognitive tasks. The authors showed more disruption of cingulum in the dysmorphic group as well. Patients with agenesis of CC have reduced volume and integrity in cingulate (Nakata et al., 2009), which underscores the entangled developmental process in these two adjacent structures. However, not all DTI studies on FASD have reported altered diffusivity pattern in cingulum. Reduced diffusivity in terms of decreased FA (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2017; Santhanam et al., 2011; Sowell et al., 2008) and increased MD and RD (O'Conaill et al., 2015; Santhanam et al., 2011) is described in the existing literature, using VBA, tract-specific, Tract-Based Spatial Statistics (TBSS), and semiautomated tractography methods. An opposite result of higher FA in FASD compared with TD is also reflected in a TBSS study by Fryer et al. (2009). Despite no reports of involvement of cingulum in math ability (Lebel et al., 2010), visuomotor integration (Sowell et al., 2008) and saccadic reaction time (Green et al., 2013), Paolozza et al. demonstrated a positive correlation between MD values of cingulum and additional saccades in eye movement control assessment in PAE. Exploratory studies by Fan et al. (2016) and Treit et al. (2013) yet did not report any diffusional differences in cingulum bundle between PAE and normally developed children. The cingulum is rather a narrow structure located between CC and cingulate cortex, two structures with different diffusion properties, which causes a challenge in DTI interpretation (Lee et al., 2009). Nevertheless, altered diffusivity in cingulum is often reported in FASD. Regarding the heterogeneity of cognitive domains declined in individuals with PAE, inconsistency in the literature may be partly due to the wide range of cognitive deficits between cohorts.

8 | BIMODAL SEX-SPECIFIC PATTERN IN THE DEVELOPMENTAL TRAJECTORY OF WHITE MATTER MICROSTRUCTURE IN FASD

DTI findings discussed above were all derived from cross-sectional studies and thus no direct conclusion can be derived about the effect of PAE

on brain developmental trajectories. Only one longitudinal DTI study by Treit et al. (2013) has examined trajectories of development in 17 children with FASD with two 3 years apart scans. They found that FA increases in all surveyed fibers in TD, but there were no changes only in the body of CC, ILF, and UF in FASD group. Group-by-age interactions showed steeper decreases of MD and perpendicular diffusivity with age in frontal lobe connective tracts, namely SLF, IFO, SFO, UF and genu in FASD, which is expected to occur in younger ages in normal status (Zhou et al., 2011). As authors have suggested, this might underscore the late catch up in regional developmental delays in FASD or compensatory plasticity, mainly through the myelination process. This is supported by the negative association observed between the quantity of longitudinal changes in MD values of SLF and scores of reading and receptive vocabulary tasks. In other words, greater longitudinal changes in diffusivity might point to the previously greater damage in the neural structure. This is also reinforced by the fact that more severe forms of FASD had more steeper decreases in MD than less severe forms of FASD than controls. However, in a recent cross-sectional study on 70 patients with FASD over 5–32 years old and with the same methodology, Treit et al. (2017) did not find any differences between DTI metrics in any of the surveyed white matter tracts between PAE and TD. Moreover, age by group interactions showed steeper increases in white matter volume and FA of the genu with age in TD and of the SLF and ILF in FASD. This in contrast shows delayed regional maturation in FASD over a longer period into adulthood. They also found that FA of SLF is reduced in males more than females with FASD compared with controls with the same gender. Although both genders had the same cognitive measures, males showed more extensive structural disruptions in terms of regional volumes and cortical thickness. Sex-specific bimodal pattern of the neural structure is well defined in animal and human studies. In this context, the role of testosterone on the organization, that is, perinatal development, and activation process, which occurs at puberty, is highlighted in determining the gender-specific neural phenotype (Blakemore, Burnett, & Dahl, 2010). Reduced sensitivity to testosterone is documented in male rats and also human male adolescents with PAE (Carter, Jacobson, Dodge, Granger, & Jacobson, 2014; Lan, Hellemans, Ellis, Viau, & Weinberg, 2009). Animal models of PAE have demonstrated the impact of dysregulated sex hormone axis on the bimodal pattern of altered brain development (Weinberg, Sliwowska, Lan, & Hellemans, 2008). The results of Treit et al. might, therefore, stem from the effect of PAE on testosterone neurophysiological functioning. This hypothesis is well addressed in another fresh DTI study by Uban et al. on adolescents using TBSS method (Uban et al., 2017). They surprisingly showed lower FA in white matter tracts in girls with PAE compared with healthy controls, while boys with PAE had higher FA relative to control boys; with no association between age and FA only in PAE boys. They also tested for the relationship between FA and gonadal hormones and revealed that boys with PAE in contrast to control boys do not exhibit any positive correlation between FA in association fibers (cingulum, IFO, SFO, and optic radiation) and level of testosterone or DHEA. Altered hormone-brain associations were also observed among girls with PAE, who showed no correlation between progesterone and FA in the fornix, as opposed to observed such positive association in control girls. Girls with PAE albeit presented a novel positive relationship between testosterone and DHEA levels and FA in SLF and CST. Selective female reductions of FA in the left SLF and left CST is replicated in the most recent study by Paolozza et al. (2017).

In sum, the complex picture of findings in PAE can stem from studying the mixture of neural developmental milestones from childhood to adulthood. It seems that neural alterations in PAE follow an ongoing process with combined delays and accelerations in neural development in different brain regions. The interference of other factors such as gonadal hormones in specific regions of the brain, which maturation relies on endocrine signals, further complicates this scenario.

9 | MICROSTRUCTURAL PATTERN RELATIVE TO THE EXTENT OF ALCOHOL EXPOSURE AND SEVERITY OF FASD

The small number of patients and lack of information regarding specific FASD diagnosis have not allowed most authors to investigate microstructural changes among different severities of FASD spectrum. However, a few studies have tried to examine diagnostic differences by comparing individuals with partial FAS/FAS to those with no facial dysmorphology. These have demonstrated a continuum of altered diffusion metrics in posterior regions of the CC (Fryer et al., 2009; Li et al., 2009), cingulum (Santhanam et al., 2011), and cerebellar peduncles (Fan et al., 2016; Spottiswoode et al., 2011), with lower FA, higher MD and RD in dysmorphic compared with nondysmorphic PAE. Among these, two studies (Fryer et al., 2009; Li et al., 2009) have explored how white matter differences across the brain may be related to the type of FASD diagnosis. The results indicate that more severe subtypes of FASD had more severe white matter damage only in the body, splenium, and isthmus of CC. This suggests that the degree of the damage to some, but not all, regions of the brain is dose-dependent. Of note, is the consistent report of mediation of RD signifying poorer myelination in this regard. In a group of children with FASD (mean age ~ 10 years old) with a positive correlation between dosage and frequency of prenatal alcohol exposure and severity of FASD, Fan et al. (2016) revealed that increased in utero alcohol exposure is related to lower FA and higher MD, more attributed to changes of RD rather than of AD, in splenium and isthmus of CC as well as in ILF. Interestingly, CC and ILF were the only structures showed to be related to IQ, which was lower among FAS patients. On the other hand, a study of the neonatal group (Taylor et al., 2015) manifested the increased axonal damage in terms of the lower AD, and to a lesser extent lower MD, with higher alcohol exposure. In this context, the timing of alcohol exposure is not evaluated yet. In fact, the correlation between the extent and timing of alcohol exposure is an important piece of the puzzle of our knowledge about FASD, which is undoubtedly difficult to assess. Furthermore, gathering data on the amount and frequency of alcohol consumption retrospectively, which is what most studies do, if they do it at all, can impose recall bias.

10 | BRAIN-BEHAVIOR RELATIONSHIP

A quite large spectrum of cognitive functions such as executive dysfunction, learning problems, memory impairment, language disorders,

lowered intelligence and visual-special deficits are well described among individuals with FASD (Coriale et al., 2013). As previously discussed, most studies have revealed the correlation between corpus callosal integrity and decline in several domains of cognition in FASD, such as processing speed, working memory, visuomotor integration, perceptual organization, math ability, and reading skills. Besides, damage to the association fibers, that is, SLF, ILF, and SFO, has been linked to reading ability (Treit et al., 2013; Treit et al., 2017) and short-term memory (Fan et al., 2016). Although most studies have focused on CC to find a brain-behavior relationship, correlation of diffusion parameters of other major white matter structures with cognitive assays has been conducted in several studies (Table 1). Taken together, it seems that interhemispheric disruption contributes to the decline in several domains of cognition in FASD, while damage to the association and projection fibers subsides fewer aspects of cognitive function. However, more studies with larger samples are needed to better specify the contribution of damage to the fiber tracts other than CC to neurocognitive dysfunction among FASD.

Searching the overlap between functional and structural connectivity is much more confirmatory than the correlation of DTI measures with behavioral scores. Among the reviewed articles only three studies have conducted fMRI and DTI techniques simultaneously on FASD cohorts and have revealed the callosal involvement in perceptual reasoning (Wozniak et al., 2011) and have confirmed the role of cingulum and ILF in attention deficits (O'Conaill et al., 2015; Santhanam et al., 2011).

11 | CONCLUSION

DTI provides sensitive measures of white matter microstructure in vivo. This technique has dramatically improved our knowledge about the altered white matter microstructure in individuals with PAE and in relation to underlying cognitive and behavioral deficits in FASD. DTI studies on individuals with PAE have thus far demonstrated reduced integrity throughout the brain compared with typically developed controls with a continuum of results regarding the extent of alcohol exposure and severity of symptoms. This is shown to be mostly reduced FA and increased MD and RD in children more than 5 years old and young adults, while changes in AD and MD are documented in newborns of alcoholic mothers. Since neonatal data point toward axonal damage, while studies on more than 5-year-old individuals more debate on myelination disruption, interpreting the results in respect of alcohol impact on epigenetics rather than cellular scale seems more consistent with these findings. Moreover, these diffusion alterations are nearly universal findings and abnormalities appear to be widespread, with no brain regions really spared. However, disruptions in the corpus callosum, especially its posterior regions, are more consistently issued among studies and in relation to dysmorphology and a wide range of cognitive deficits. Although one study failed to find any significant association between cognitive test scores and DTI metrics, multiple studies have proved different aspects of neurobehavioral maldevelopment correlated to pathologies in specific white matter regions.

Examining age and sex interaction with DTI findings has revealed interesting results. It seems that prenatal alcohol exposure delays the maturation of axonal tracts, mostly through disruptions in myelination process, along with a possible late catch up in frontal association fibers before puberty. Compensating for disrupted formation/maturation of neural tracts and relying on an irrelevant structure is replicated in several studies. Nevertheless, increased integrity has not always allowed for complete resolution of cognitive deficits. The effect of ethanol on gonadal hormone pathway has also resulted in bimodal sex pattern in the developmental trajectory of white matter in FASD, most commonly in the longitudinal fasciculi.

Caution should be exercised interpreting these results, as they are derived from small samples of patients with a wide range of ages. Furthermore, cofactors such as consumption of and/or prenatal exposure to of other illicit drugs are not fully investigated. Except for one longitudinal study over a small range of prepubertal stage, other studies have a cross-sectional design to determine the altered white matter integrities in individuals with PAE. However, the target of in-utero alcohol exposure is an immature brain with resulted ongoing disruptive pathology through neurodevelopmental stages. Thus, longitudinal studies with large sample sizes, especially in critical developmental periods such as perinatal and pubertal stages are clearly needed to track the insults of alcohol on the developing neural structures. Future research will also benefit from examining the effect of PAE on hemispheric lateralization. One important pitfall is the knowledge about the timing of exposure which cannot be readily assessed in humans concerning moral issues.

Even though the tensor technique is a valid and time-efficient procedure to investigate brain microstructural architecture in pediatrics, the results can be affected by inherent limitations. Apart from fully inevitable noises and artifacts, the evidence is gathered indirectly in this technique and exact types of cell damage cannot be precisely distinguished. DTI assumes only one fiber bundle in each voxel and thus crossing fibers have been always considered as a potential source of inaccuracy in this method. By simply adopting multiple fiber projections within a voxel, high angular resolution diffusion imaging (HARDI), although a more time-consuming acquisition protocol, has overcome this shortage. Diffusional kurtosis imaging (DKI) (Jensen & Helpern, 2010) is an extension model of DTI and serves as another solution in intravoxel fiber crossing imprecisions. DKI is clinically operable in a total of 10 min (Lu, Jensen, Ramani, & Helpern, 2006). Besides, another diffusion MRI technique, neurite orientation dispersion and density imaging (NODDI) has proved to be efficiently more sensitive and specific to microstructural alterations than the tensor model. NODDI is applicable to neonates by applying limited orientations. This will shrink the standard 30 min needed to acquire the imaging to only 10 min (Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). NODDI also provides the extent of neural development by means of increased dispersion of neurite orientation distribution. Another advantage of this modality to assess neurodevelopmental disorders such as FASD (Zhang et al., 2012). Accordingly, these new modes of diffusion imaging analyses should be considered in future studies.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

This article does not contain any part with the requirement of informed consent for subjects.

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REFERENCES

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Fiber composition of the human corpus callosum. *Brain Research*, *598*, 143–153.

Adam, G. (2016) *Corpus callosum: Embryological development, anomalies and their imaging presentation.* Poster No.: C-0496. In European Congress of Radiology 2017.

Agosta, F., Galantucci, S., & Filippi, M. (2017). Advanced magnetic resonance imaging of neurodegenerative diseases. *Neurological Sciences*, *38*, 41–51.

Alexander, A. L., Hasan, K., Kindlmann, G., Parker, D. L., & Tsuruda, J. S. (2000). A geometric analysis of diffusion tensor measurements of the human brain. *Magnetic Resonance in Medicine*, *44*, 283–291.

Archibald, S. L., Fennema-Notestine, C., Gamst, A., Riley, E. P., Mattson, S. N., & Jernigan, T. L. (2001). Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Developmental Medicine and Child Neurology*, *43*, 148–154.

Astley, S. J. (2004). *Diagnostic guide for fetal alcohol spectrum disorders: The 4-digit diagnostic code*. Washington, DC: University of Washington.

Astley, S. J., Aylward, E. H., Olson, H. C., Kerns, K., Brooks, A., Coggins, T. E., … Jirikowic, T. (2009). Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research*, *33*, 1671–1689.

Aung, W. Y., Mar, S., & Benzinger, T. L. (2013). Diffusion tensor MRI as a biomarker in axonal and myelin damage. *Imaging in Medicine*, *5*, 427–440.

Autti-Ramo, I. (2002). Foetal alcohol syndrome: A multifaceted condition. *Developmental Medicine and Child Neurology*, *44*, 141–144.

Autti-Rämö, I., Autti, T., Korkman, M., Kettunen, S., Salonen, O., & Valanne, L. (2002). MRI findings in children with school problems who had been exposed prenatally to alcohol. *Developmental Medicine and Child Neurology*, *44*, 98–106.

Baillieux, H., De Smet, H. J., Dobbeleir, A., Paquier, P. F., De Deyn, P. P., & Mariën, P. (2010). Cognitive and affective disturbances following focal cerebellar damage in adults: A neuropsychological and SPECT study. *Cortex*, *46*, 869–879.

Barr, H. M., & Streissguth, A. P. (2001). Identifying maternal self-reported alcohol use associated with fetal alcohol spectrum disorders. *Alcoholism, Clinical and Experimental Research*, *25*, 283–287.

Basser, P. J., & Jones, D. K. (2002). Diffusion-tensor MRI: Theory, experimental design and data analysis: A technical review. *NMR in Biomedicine*, *15*, 456–467.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system: A technical review. *NMR in Biomedicine*, *15*, 435–455.

Benjamins, J. A., Nedelkoska, L., Lisak, R. P., Hannigan, J. H., & Sokol, R. J. (2011). Cytokines reduce toxic effects of ethanol on oligodendroglia. *Neurochemical Research*, *36*, 1677–1686.

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping*, *31*, 926–933.

Bookstein, F. L., Connor, P. D., Huggins, J. E., Barr, H. M., Pimentel, K. D., & Streissguth, A. P. (2007). Many infants prenatally exposed to high levels of alcohol show one particular anomaly of the corpus callosum. *Alcoholism: Clinical and Experimental Research*, *31*, 868–879.

Bookstein, F. L., Sampson, P. D., Connor, P. D., & Streissguth, A. P. (2002). Midline corpus callosum is a neuroanatomical focus of fetal alcohol damage. *The Anatomical Record*, *269*, 162–174.

Bookstein, F. L., Streissguth, A. P., Sampson, P. D., Connor, P. D., & Barr, H. M. (2002). Corpus callosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. *NeuroImage*, *15*, 233–251.

Carter, R. C., Jacobson, J. L., Dodge, N. C., Granger, D. A., & Jacobson, S. W. (2014). Effects of prenatal alcohol exposure on testosterone and pubertal development. *Alcoholism: Clinical and Experimental Research*, *38*, 1671–1679.

Clarren, S. K., Alvord, E. C., Sumi, S. M., Streissguth, A. P., & Smith, D. W. (1978). Brain malformations related to prenatal exposure to ethanol. *The Journal of Pediatrics*, *92*, 64–67.

Clarren, S. K., & Smith, D. W. (1978). The fetal alcohol syndrome. *The Lamp*, *35*, 4–7.

Colby, J. B., Smith, L., O'Connor, M. J., Bookheimer, S. Y., Van Horn, J. D., & Sowell, E. R. (2012). White matter microstructural alterations in children with prenatal methamphetamine/polydrug exposure. *Psychiatry Research: Neuroimaging*, *204*, 140–148.

Concha, L. (2014). A macroscopic view of microstructure: Using diffusion-weighted images to infer damage, repair, and plasticity of white matter. *Neuroscience*, *276*, 14–28.

Coriale, G., Fiorentino, D., Di Lauro, F., Marchitelli, R., Scalese, B., Fiore, M., … Ceccanti, M. (2013). Fetal alcohol Spectrum disorder (FASD): Neurobehavioral profile, indications for diagnosis and treatment. *Rivista di Psichiatria*, *48*, 359–369.

Coulter, C. L., Leech, R. W., Schaefer, G. B., Scheithauer, B. W., & Brumback, R. A. (1993). Midline cerebral dysgenesis, dysfunction of the hypothalamic-pituitary axis, and fetal alcohol effects. *Archives of Neurology*, *50*, 771–775.

Crepin, G., Dehaene, P., & Samaille, C. (1989). Clinical aspects, epidemiologic progression of fetal alcoholism: A current daily problem. *Bulletin de l'Academie Nationale de Medecine*, *173*, 575–582 discussion 582–585.

Cudd, T. A. (2005). Animal model systems for the study of alcohol teratology. *Experimental Biology and Medicine*, *230*, 389–393.

Domellöf, E., Rönnqvist, L., Titran, M., Esseily, R., & Fagard, J. (2009). Atypical functional lateralization in children with fetal alcohol syndrome. *Developmental Psychobiology*, *51*, 696–705.

Donald, K. A., Roos, A., Fouche, J. P., Koen, N., Howells, F. M., Woods, R. P., … Stein, D. J. (2015). A study of the effects of prenatal alcohol exposure on white matter microstructural integrity at birth. *Acta Neuropsychiatrica*, *27*, 197–205.

Engelbrecht, V., Scherer, A., Rassek, M., Witsack, H. J., & Modder, U. (2002). Diffusion-weighted MR imaging in the brain in children: Findings in the normal brain and in the brain with white matter diseases. *Radiology*, *222*, 410–418.

Fan, J., Jacobson, S. W., Taylor, P. A., Molteno, C. D., Dodge, N. C., Stanton, M. E., … Meintjes, E. M. (2016). White matter deficits mediate effects of prenatal alcohol exposure on cognitive development in childhood. *Human Brain Mapping*, *37*, 2943–2958.

Fryer, S. L., Schweinsburg, B. C., Bjorkquist, O. A., Frank, L. R., Mattson, S. N., Spadoni, A. D., & Riley, E. P. (2009). Characterization of white matter microstructure in fetal alcohol spectrum disorders. *Alcoholism, Clinical and Experimental Research*, *33*, 514–521.

Goodlett, C. R., Horn, K. H., & Zhou, F. C. (2005). Alcohol teratogenesis: Mechanisms of damage and strategies for intervention. *Experimental Biology and Medicine*, *230*, 394–406.

Goodlett, C. R., Marcussen, B. L., & West, J. R. (1990). A single day of alcohol exposure during the brain growth spurt induces brain weight restriction and cerebellar Purkinje cell loss. *Alcohol (Fayetteville, NY)*, *7*, 107–114.

Green, C. R., Lebel, C., Rasmussen, C., Beaulieu, C., & Reynolds, J. N. (2013). Diffusion tensor imaging correlates of saccadic reaction time in children with fetal alcohol spectrum disorder. *Alcoholism, Clinical and Experimental Research*, *37*, 1499–1507.

Guerri, C., Bazinet, A., & Riley, E. P. (2009). Foetal alcohol spectrum disorders and alterations in brain and behaviour. *Alcohol & Alcoholism*, *44*, 108–114.

Guerri, C., Pascual, M. A., & Renau-Piqueras, J. (2001). Glia and fetal alcohol syndrome. *Neurotoxicology*, *22*, 593–599.

Hamre, K. M., & West, J. R. (1993). The effects of the timing of ethanol exposure during the brain growth spurt on the number of cerebellar Purkinje and granule cell nuclear profiles. *Alcoholism: Clinical and Experimental Research*, *17*, 610–622.

Hellige, J. B. (1993). *Hemispheric asymmetry: What's right and what's left*. Cambridge, MA: Harvard University Press.

Hill, R. M., Hegemier, S., & Tennyson, L. M. (1989). The fetal alcohol syndrome: A multihandicapped child. *Neurotoxicology*, *10*, 585–595.

Huang, H., Zhang, J., Jiang, H., Wakana, S., Poetscher, L., Miller, M. I., … Mori, S. (2005). DTI tractography based parcellation of white matter: Application to the mid-sagittal morphology of corpus callosum. *NeuroImage*, *26*, 195–205.

Huppi, P. S., Maier, S. E., Peled, S., Zientara, G. P., Barnes, P. D., Jolesz, F. A., & Volpe, J. J. (1998). Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatric Research*, *44*, 584–590.

Jensen, J. H., & Helpern, J. A. (2010). MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR in Biomedicine*, *23*, 698–710.

Jones, K., & Smith, D. (1973). Recognition of the fetal alcohol syndrome in early infancy. *The Lancet*, *302*, 999–1001.

Kinney, H., Faix, R., & Brazy, J. (1980). The fetal alcohol syndrome and neuroblastoma. *Pediatrics*, *66*, 130–132.

Lan, N., Hellemans, K. G., Ellis, L., Viau, V., & Weinberg, J. (2009). Role of testosterone in mediating prenatal ethanol effects on hypothalamic–pituitary–adrenal activity in male rats. *Psychoneuroendocrinology*, *34*, 1314–1328.

Lebel, C., Rasmussen, C., Wyper, K., Andrew, G., & Beaulieu, C. (2010). Brain microstructure is related to math ability in children with fetal alcohol spectrum disorder. *Alcoholism, Clinical and Experimental Research*, *34*, 354–363.

Lebel, C., Rasmussen, C., Wyper, K., Walker, L., Andrew, G., Yager, J., & Beaulieu, C. (2008). Brain diffusion abnormalities in children with fetal alcohol spectrum disorder. *Alcoholism, Clinical and Experimental Research*, *32*, 1732–1740.

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*, 1044–1055.

Lee, J. E., Chung, M. K., Lazar, M., DuBray, M. B., Kim, J., Bigler, E. D., … Alexander, A. L. (2009). A study of diffusion tensor imaging by tissue-specific, smoothing-compensated voxel-based analysis. *NeuroImage*, *44*, 870–883.

Leigh, R. J., & Zee, D. S. (2015). *The neurology of eye movements*. New York, NY: Oxford University Press.

Lemoine, P. (1992). Outcome of children of alcoholic mothers [study of 105 cases followed to adult age] and various prophylactic findings. *Annals of Pediartics*, *39*, 226–235.

Li, L., Coles, C. D., Lynch, M. E., & Hu, X. (2009). Voxelwise and skeleton-based region of interest analysis of fetal alcohol syndrome and fetal alcohol spectrum disorders in young adults. *Human Brain Mapping*, *30*, 3265–3274.

Lu, H., Jensen, J. H., Ramani, A., & Helpern, J. A. (2006). Three-dimensional characterization of non-gaussian water diffusion in humans using diffusion kurtosis imaging. *NMR in Biomedicine*, *19*, 236–247.

Ma, X., Coles, C. D., Lynch, M. E., Laconte, S. M., Zurkiya, O., Wang, D., & Hu, X. (2005). Evaluation of corpus callosum anisotropy in young adults with fetal alcohol syndrome according to diffusion tensor imaging. *Alcoholism, Clinical and Experimental Research*, *29*, 1214–1222.

Maier, S. E., Miller, J. A., Blackwell, J. M., & West, J. R. (1999). Fetal alcohol exposure and temporal vulnerability: Regional differences in cell loss as a function of the timing of binge-like alcohol exposure during brain development. *Alcoholism: Clinical and Experimental Research*, *23*, 726–734.

Maier, S. E., & West, J. R. (2001). Regional differences in cell loss associated with binge-like alcohol exposure during the first two trimesters equivalent in the rat. *Alcohol (Fayetteville, NY)*, *23*, 49–57.

Malisza, K. L., Allman, A. A., Shiloff, D., Jakobson, L., Longstaffe, S., & Chudley, A. E. (2005). Evaluation of spatial working memory function in children and adults with fetal alcohol spectrum disorders: A functional magnetic resonance imaging study. *Pediatric Research*, *58*, 1150–1157.

Mattson, S. N., Riley, E. P., Sowell, E. R., Jernigan, T. L., Sobel, D. F., & Jones, K. L. (1996). A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcoholism, Clinical and Experimental Research*, *20*, 1088–1093.

McGee, C. L., & Riley, E. P. (2006). Brain imaging and fetal alcohol spectrum disorders. *Annali dell'Istituto Superiore di Sanitã*, *42*, 46–52.

Moncrieff, D. W. (2010). Hemispheric asymmetry in pediatric developmental disorders: Autism, attention-deficit/hyperactivity disorder, and dyslexia. In K. Hugdahl & R. Westerhausen (Eds.), *The two halves of the brain* (pp. 561–601). Cambridge, MA: MIT Press.

Mukherjee, R. A., Hollins, S., & Turk, J. (2006). Fetal alcohol spectrum disorder: An overview. *Journal of the Royal Society of Medicine*, *99*, 298–302.

Müri, R. M., & Nyffeler, T. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain and Cognition*, *68*, 284–292.

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*, 1227–1233.

Nakata, Y., Barkovich, A., Wahl, M., Strominger, Z., Jeremy, R., Wakahiro, M., … Sherr, E. (2009). Diffusion abnormalities and reduced volume of the ventral cingulum bundle in agenesis of the corpus callosum: A 3T imaging study. *American Journal of Neuroradiology*, *30*, 1142–1148.

Napper, R., & West, J. R. (1995). Permanent neuronal cell loss in the cerebellum of rats exposed to continuous low blood alcohol levels during the brain growth spurt: A stereological investigation. *Journal of Comparative Neurology*, *362*, 283–292.

Neil, J., Miller, J., Mukherjee, P., & Huppi, P. S. (2002). Diffusion tensor imaging of normal and injured developing human brain: A technical review. *NMR in Biomedicine*, *15*, 543–552.

Nyffeler, T., Müri, R., Pflugshaupt, T., Wartburg, R., & Hess, C. W. (2006). Cortical reorganization after brain damage: The oculomotor model. *European Journal of Neuroscience*, *23*, 1397–1402.

O'Conaill, C. R., Malisza, K. L., Buss, J. L., Bolster, R. B., Clancy, C., de Gervai, P. D., … Longstaffe, S. (2015). Visual search for feature conjunctions: An fMRI study comparing alcohol-related neurodevelopmental disorder (ARND) to ADHD. *Journal of Neurodevelopmental Disorders*, *7*, 10.

O'Leary-Moore, S. K., Parnell, S. E., Lipinski, R. J., & Sulik, K. K. (2011). Magnetic resonance-based imaging in animal models of fetal alcohol spectrum disorder. *Neuropsychology Review*, *21*, 167–185.

Ozer, E., Sarioglu, S., & Güre, A. (2000). Effects of prenatal ethanol exposure on neuronal migration, neuronogenesis and brain myelination in the mice brain. *Clinical Neuropathology*, *19*, 21–25.

Paolozza, A., Rasmussen, C., Pei, J., Hanlon-Dearman, A., Nikkel, S. M., Andrew, G., … Reynolds, J. N. (2014a). Deficits in response inhibition correlate with oculomotor control in children with fetal alcohol spectrum disorder and prenatal alcohol exposure. *Behavioural Brain Research*, *259*, 97–105.

Paolozza, A., Rasmussen, C., Pei, J., Hanlon-Dearman, A., Nikkel, S. M., Andrew, G., … Reynolds, J. N. (2014b). Working memory and visuospatial deficits correlate with oculomotor control in children with fetal alcohol spectrum disorder. *Behavioural Brain Research*, *263*, 70–79.

Paolozza, A., Treit, S., Beaulieu, C., & Reynolds, J. N. (2014). Response inhibition deficits in children with fetal alcohol Spectrum disorder: Relationship between diffusion tensor imaging of the corpus callosum and eye movement control. *NeuroImage Clinical*, *5*, 53–61.

Paolozza, A., Treit, S., Beaulieu, C., & Reynolds, J. N. (2017). Diffusion tensor imaging of white matter and correlates to eye movement control

and psychometric testing in children with prenatal alcohol exposure. *Human Brain Mapping*, *38*, 444–456.

Peiffer, J., Majewski, F., Fischbach, H., Bierich, J. R., & Volk, B. (1979). Alcohol embryo- and fetopathy. Neuropathology of 3 children and 3 fetuses. *Journal of the Neurological Sciences*, *41*, 125–137.

Pfeiffer, J., Majewski, F., Fischbach, H., Bierich, J., & Volk, B. (1979). Alcohol embryo-and fetopathy. *Journal of the Neurological Sciences*, *41*, 125–137.

Phillips, D., & Krueger, S. (1992). Effects of combined pre-and postnatal ethanol exposure (three trimester equivalency) on glial cell development in rat optic nerve. *International Journal of Developmental Neuroscience*, *10*, 197–206.

Riley, E. P., Mattson, S. N., Sowell, E. R., Jernigan, T. L., Sobel, D. F., & Jones, K. L. (1995). Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research*, *19*, 1198–1202.

Roebuck, T. M., Mattson, S. N., & Riley, E. P. (1998). A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism: Clinical and Experimental Research*, *22*, 339–344.

Roussotte, F., Soderberg, L., & Sowell, E. (2010). Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: Evidence from neuroimaging. *Neuropsychology Review*, *20*, 376–397.

Roussotte, F. F., Sulik, K. K., Mattson, S. N., Riley, E. P., Jones, K. L., Adnams, C. M., … Sowell, E. R. (2012). Regional brain volume reductions relate to facial dysmorphology and neurocognitive function in fetal alcohol spectrum disorders. *Human Brain Mapping*, *33*, 920–937.

Santhanam, P., Coles, C. D., Li, Z., Li, L., Lynch, M. E., & Hu, X. (2011). Default mode network dysfunction in adults with prenatal alcohol exposure. *Psychiatry Research: Neuroimaging*, *194*, 354–362.

Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2005). Cognitive functions correlate with white matter architecture in a normal pediatric population: A diffusion tensor MRI study. *Human Brain Mapping*, *26*, 139–147.

Sharpe, J. A., Bondar, R. L., & Fletcher, W. A. (1985). Contralateral gaze deviation after frontal lobe haemorrhage. *Journal of Neurology, Neurosurgery & Psychiatry*, *48*, 86–88.

Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, *26*, 132–140.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage*, *17*, 1429–1436.

Sowell, E. R., Jernigan, T. L., Mattson, S. N., Riley, E. P., Sobel, D. F., & Jones, K. L. (1996). Abnormal development of the cerebellar vermis in children prenatally exposed to alcohol: Size reduction in lobules I–V. *Alcoholism: Clinical and Experimental Research*, *20*, 31–34.

Sowell, E. R., Johnson, A., Kan, E., Lu, L. H., Van Horn, J. D., Toga, A. W., … Bookheimer, S. Y. (2008). Mapping white matter integrity and neurobehavioral correlates in children with fetal alcohol Spectrum disorders. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*, 1313–1319.

Sowell, E. R., Mattson, S., Thompson, P., Jernigan, T., Riley, E., & Toga, A. (2001). Mapping callosal morphology and cognitive correlates effects of heavy prenatal alcohol exposure. *Neurology*, *57*, 235–244.

Sowell, E. R., Mattson, S. N., Kan, E., Thompson, P. M., Riley, E. P., & Toga, A. W. (2007). Abnormal cortical thickness and brain–behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cerebral Cortex*, *18*, 136–144.

Sowell, E. R., Thompson, P. M., Peterson, B. S., Mattson, S. N., Welcome, S. E., Henkenius, A. L., … Toga, A. W. (2002). Mapping cortical gray matter asymmetry patterns in adolescents with heavy prenatal alcohol exposure. *NeuroImage*, *17*, 1807–1819.

Spottiswoode, B. S., Meintjes, E. M., Anderson, A. W., Molteno, C. D., Stanton, M. E., Dodge, N. C., … Jacobson, S. W. (2011). Diffusion tensor imaging of the cerebellum and eyeblink conditioning in fetal alcohol spectrum disorder. *Alcoholism: Clinical and Experimental Research*, *35*, 2174–2183.

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, *25*, 603–605.

Sulik, K. K. (2005). Genesis of alcohol-induced craniofacial dysmorphism. *Experimental Biology and Medicine*, *230*, 366–375.

Taylor, P. A., Jacobson, S. W., van der Kouwe, A., Molteno, C. D., Chen, G., Wintermark, P., … Meintjes, E. M. (2015). A DTI-based tractography study of effects on brain structure associated with prenatal alcohol exposure in newborns. *Human Brain Mapping*, *36*, 170–186.

Thomas, J. D., Goodlett, C. R., & West, J. R. (1998). Alcohol-induced Purkinje cell loss depends on developmental timing of alcohol exposure and correlates with motor performance. *Developmental Brain Research*, *105*, 159–166.

Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *Focus*, *4*, 378–390.

Treit, S., Chen, Z., Zhou, D., Baugh, L., Rasmussen, C., Andrew, G., … Beaulieu, C. (2017). Sexual dimorphism of volume reduction but not cognitive deficit in fetal alcohol spectrum disorders: A combined diffusion tensor imaging, cortical thickness and brain volume study. *NeuroImage: Clinical*, *15*, 284–297.

Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., & Beaulieu, C. (2013). Longitudinal MRI reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *33*, 10098–10109.

Uban, K., Herting, M., Wozniak, J., & Sowell, E. (2017). Sex differences in associations between white matter microstructure and gonadal hormones in children and adolescents with prenatal alcohol exposure. *Psychoneuroendocrinology*, *83*, 111–121.

Ungerer, M., Knezovich, J., & Ramsay, M. (2013). In utero alcohol exposure, epigenetic changes, and their consequences. *Alcohol Research: Current Reviews*, *35*, 37.

Weinberg, J., Sliwowska, J. H., Lan, N., & Hellemans, K. (2008). Prenatal alcohol exposure: Foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. *Journal of Neuroendocrinology*, *20*, 470–488.

West, J. (1993). Acute and long-term changes in the cerebellum following developmental exposure to ethanol. *Alcohol and Alcoholism (Oxford, Oxfordshire)*, *2*, 199–202.

Wheeler-Kingshott, C. A., & Cercignani, M. (2009). About "axial" and "radial" diffusivities. *Magnetic Resonance in Medicine*, *61*, 1255–1260.

Wisniewski, K., Dambska, M., Sher, J., & Qazi, Q. (1983). A clinical neuropathological study of the fetal alcohol syndrome. *Neuropediatrics*, *14*, 197–201.

Wozniak, J. R., Mueller, B. A., Chang, P. N., Muetzel, R. L., Caros, L., & Lim, K. O. (2006). Diffusion tensor imaging in children with fetal alcohol spectrum disorders. *Alcoholism, Clinical and Experimental Research*, *30*, 1799–1806.

Wozniak, J. R., Mueller, B. A., Muetzel, R. L., Bell, C. J., Hoecker, H. L., Nelson, M. L., … Lim, K. O. (2011). Inter-hemispheric functional connectivity disruption in children with prenatal alcohol exposure. *Alcoholism, Clinical and Experimental Research*, *35*, 849–861.

Wozniak, J. R., Muetzel, R. L., Mueller, B. A., McGee, C. L., Freerks, M. A., Ward, E. E., … Lim, K. O. (2009). Microstructural corpus callosum anomalies in children with prenatal alcohol exposure: An extension of previous diffusion tensor imaging findings. *Alcoholism, Clinical and Experimental Research*, *33*, 1825–1835.

Yang, Y., Roussotte, F., Kan, E., Sulik, K. K., Mattson, S. N., Riley, E. P., … O'connor, M. J. (2011). Abnormal cortical thickness alterations in fetal alcohol spectrum disorders and their relationships with facial dysmorphology. *Cerebral Cortex*, *22*, 1170–1179.

Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012). NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, *61*, 1000–1016.

Zhou, D., Lebel, C., Lepage, C., Rasmussen, C., Evans, A., Wyper, K., … Beaulieu, C. (2011). Developmental cortical thinning in fetal alcohol spectrum disorders. *NeuroImage*, *58*, 16–25.

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