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Radial and tangential neuronal migration pathways in the human fetal brain: Anatomically distinct patterns of diffusion MRI coherence

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ABSTRACT

Corticogenesis is underpinned by a complex process of subcortical neuroproliferation, followed by highly orchestrated cellular migration. A greater appreciation of the processes involved in human fetal corticogenesis is vital to gaining an understanding of how developmental disturbances originating in gestation could establish a variety of complex neuropathology manifesting in childhood, or even in adult life. Magnetic resonance imaging modalities offer a unique insight into anatomical structure, and increasingly infer information regarding underlying microstructure in the human brain. In this study we applied a combination of high-resolution structural and diffusion-weighted magnetic resonance imaging to a unique cohort of three post-mortem fetal brain specimens, aged between 19 and 22 post-conceptual weeks. Specifically, we sought to assess patterns of diffusion coherence associated with subcortical neuroproliferative structures: the pallial ventricular/subventricular zone and subpallial ganglionic eminence. Two distinct three-dimensional patterns of diffusion coherence were evident: a clear radial pattern originating in ventricular/subventricular zone, and a tangentio-radial patterns originating in ganglionic eminence. These patterns appeared to regress in a caudo-rostral and lateral-ventral to medial-dorsal direction across the short period of fetal development under study. Our findings demonstrate for the first time distinct patterns of diffusion coherence associated with known anatomical proliferative structures. The radial pattern associated with dorsopallial ventricular/subventricular zone and the tangentio-radial pattern associated with subpallial ganglionic eminence are consistent with reports of radial–glial mediated neuronal migration pathways identified during human corticogenesis, supported by our prior studies of comparative fetal diffusion MRI and histology. The ability to assess such pathways in the fetal brain using MR imaging offers a unique insight into three-dimensional trajectories beyond those visualized using traditional histological techniques. Our results suggest that *ex-vivo* fetal MRI is a potentially useful modality in understanding normal human development and various disease processes whose etiology may originate in aberrant fetal neuronal migration.

Introduction

The cerebral cortex is a highly conserved, six-layered structure, thought to bestow advanced cognitive and intellectual abilities in humans (Lui et al., 2011; Rakic, 2009). The cellular constituents of the cortex are generated in the ventricular/subventricular transient embryonic zones and subpallial ganglionic eminence (GE) during fetal development (Ayoub et al., 2011; Parnavelas et al., 2002; Petanjek et al., 2009a,b; Ulfig et al., 2000), with an ensuing process of highly orchestrated cellular migration along transient glial cell scaffold structures to establish cortical structure (Bystron et al., 2008; Marín and Rubenstein, 2001, 2003; Sild and Ruthazer, 2011). Cortical dysfunction is implicated in a range of human disease processes, with an increasing emphasis on aberrancies originating during neurodevelopment (Francis et al., 2006; Manzini and Walsh, 2011). A greater appreciation of the processes involved in corticogenesis is therefore vital to gain an understanding of how developmental disturbances originating in gestation could establish a complex neuropathology, which may not manifest until childhood or even in adult life.

During corticogenesis neuronal subtypes differ in both their origins and migrational trajectories. Excitatory glutamatergic projection neurons follow the radial unit hypothesis, originating in the proliferative dorsopallial ventricular/subventricular zone, and migrating along radial

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glial fascicles to the cortical plate (Bystron et al., 2008; Rakic, 1972, 1988). The ventricular/subventricular proliferative zone effectively forms a protomap translated into columnar cortical structure via a highly organized process of radial migration. In contrast, cortical inhibitory GABAergic interneurons are more diverse in terms of their proliferative origins and follow more complex migratory routes that are at times tangential to the cortical plate (Wonders and Anderson, 2006). GABAergic inhibitory interneurons account for 25–30% of the cortical neuronal population in primates (Hendry et al., 1987), and dysfunction therein has been implicated in a range of neurological and psychiatric disorders (Benes and Berretta, 2001; Gressens, 2006; Marín, 2012; Volpe, 2009). A greater appreciation of these tangential neuronal migratory patterns, along with their radial counterparts, is therefore crucial to a full understanding of human corticogenesis and the potential aberrations therein that could lead to cortical dysfunction.

Early studies of non-radial migration patterns undertaken in rodent and ferret established a tangential pattern in clear contrast to the radial unit hypothesis proposed for excitatory glutamatergic neuronal migration (DeDiego et al., 1994; O'Rourke et al., 1992, 1995). This pattern of migration followed a trajectory initially tangential to the cortical plate, before assuming a radial pathway through the intermediate zone towards the cortical surface. Further investigation in murine systems implicated this pattern in the development of GABAergic interneurons originating from the subpallial ganglionic eminence (Anderson et al., 1997, 2001; De Carlos et al., 1996; Tamamaki et al., 1997; Wichterle et al., 1999; Wichterle et al., 2001) yielding a dualistic model in which cortical projection neurons were thought to migrate radially, and cortical interneurons were thought to migrate initially tangential to the cortical surface before following a radial route (Anderson et al., 2002). However, a landmark study assessing GABAergic migratory streams in slice cultures of embryonic human forebrain identified two distinct GABAergic lineages: one radially migrating, $Mash1^{+}$ expressing lineage originating from the neocortical dorsopallial ventricular/subventricular zone, and a second $Dlx1/2^{+}/Mash1^{-}$ group initially migrating tangentially from the subpallial ganglionic eminence (Jakovcevski et al., 2011; Letinic et al., 2002) (Fig. 1). This finding and subsequent investigations of corticogenesis in primates have prompted a reappraisal of neuronal migration and assumptions made from murine models (Jones, 2009; Petanjek et al., 2009a,b).

While the murine brain offers a characteristic six-layered mammalian cerebral cortex and considerable potential for transgenic manipulation, lineage continuity does not exist between mouse and man (Murphy et al., 2004). The mouse brain shows distinct differences in the relative proportions of GABAergic interneurons and the variety of specific subtypes present (White and Keller, 1989; Yáñez et al., 2005). Radially migrating GABAergic neurons originating dorsopallial ventricular zone (VZ) are a recent development evolutionarily, observed in primates and humans but not in mice (Petanjek et al., 2009b; Reinchisi et al., 2012; Tanaka and Nakajima, 2012; Zecevic et al., 2011). Given the clear distinction between murine and primate migratory patterns, and recent evidence suggesting that certain aspects of neuronal migration are unique to human corticogenesis (Letinic and Rakic, 2001), there is a clear necessity to investigate migratory patterns directly in the human brain.

Surprisingly there is little information available about human corticogenesis and the spatiotemporal features of radial and tangential migration streams. Recent efforts have focused on the rostral migratory stream and the potential postnatal proliferative viability of neuroblasts therein (Sanai et al., 2011; van Strien et al., 2011; Wang et al., 2011). However, due to limitations inherent to microscopic studies, only small regions of this, and other migratory streams can be investigated through histological assessment alone. A more systematic assessment of the migratory streams present at any fetal stage is still lacking.

Magnetic resonance imaging offers the unique ability to assess neuroanatomical structure non-invasively through underlying tissue characteristics across the entire brain. *Ex-vivo* structural MRI can detect subtle anatomical detail in control and pathological specimens, with resolution in the order of micrometers increasingly attainable (Fischl et al., 2009). Tissue organization can be further probed using diffusion-weighted magnetic resonance imaging (DW-MRI): a modality sensitive to the diffusion patterns of free water, with signal thus reflecting the constraints imposed on water movement by underlying tissue structure such as white matter fiber bundles (Beaulieu, 2002). DW-MRI is useful in inferring information regarding underlying brain microstructure, even in fixed pathological specimens (Kolasinski et al., 2012; Miller et al., 2011). *Ex-vivo* DW-MRI can typically attain a spatial resolution as great as 500 μm isotropic. Recently DW-MRI was shown to be sensitive to underlying tissue

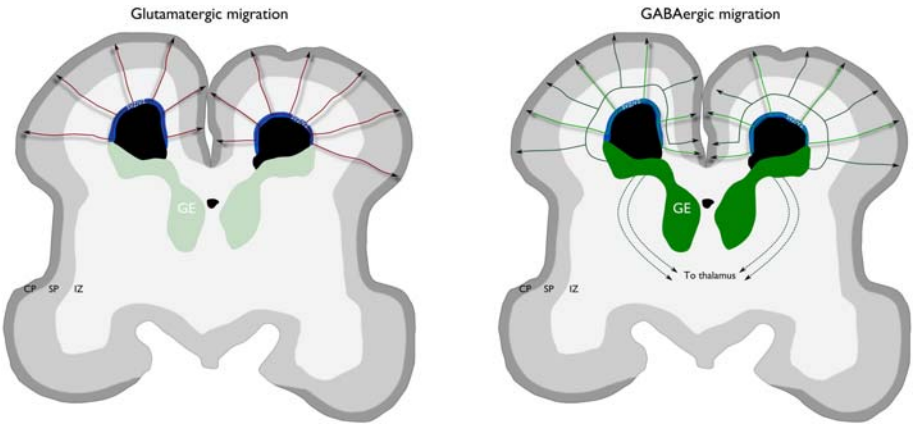


Fig. 1. Radial and tangential routes of GABA-ergic and glutamatergic neuronal migration in the human fetal brain. Simplified two-dimensional schematic representations of the pallial and subpallial origins and migratory routes of two major classes of cortical neurons. Glutamatergic neurons originate in the pallial ventricular zone/subventricular zone (blue), with some tangential migration within the SVZ/VZ, but a dominant pattern of radial migration along radial glial fascicles in a plane perpendicular to the orientation of the cortical plate (radial pathways: blue arrows). GABA-ergic neurons in the human brain originate from both pallial ventricular zone/subventricular zone (blue) and subpallial ganglionic eminence (green). GABA-ergic neurons from ganglionic eminence display a pattern of migration initially tangential to the orientation of the cortical surface, before assuming a radial trajectory in intermediate zone towards the cortical plate (tangential pathway: dark green arrows); a pattern reported in more diverse mammalian systems. A pattern of GABAergic neuronal migration originating in SVZ/VZ and displaying a radial trajectory to cortical plate has been reported more recently in humans and non-human primates (light green arrows). GABA-ergic neurons originating from ganglionic eminence also migrate via subcortical paths to thalamus. Migratory pathways are displayed on a schematic slice of frontal cortex from a human fetus at 19 post-conceptual weeks. GE: ganglionic eminence; VZ: ventricular zone; SVZ: subventricular zone; IZ: intermediate zone; SP: subplate; CP: cortical plate.

microstructure in fixed human fetal brains, with strong evidence suggesting radial glial fiber orientation as a driving force behind the observed patterns of diffusion anisotropy (Takahashi et al., 2012; Xu et al., 2012). However, these studies were limited by a lack of structural MRI data and did not perform a detailed analysis of the temporal and regional variation in the migratory pathways of the fetal brain.

In order to assess global patterns of neuronal migration during human neurodevelopment, we apply a combination of high-resolution structural and diffusion-weighted magnetic resonance imaging to a unique cohort of three post-mortem fetal brain specimens between 19 and 22 post-conceptual weeks (pcw): a period of intense neuronal proliferation and migration (Sidman and Rakic, 1973) (Table 1). Using this multimodal approach, we consider two key structures based on their documented involvement in human neuronal proliferation and migration: GABA-ergic subpallial ganglionic eminence (GE), and GABAergic/glutamatergic dorsopallial ventricular/subventricular zone (VZ) (Petanjek et al., 2009b) (Fig. 1). Our primary aim was to use diffusion tensor imaging and tractography to assess patterns of diffusion coherence associated with these anatomical structures. In particular, we hypothesize that the diffusion patterns associated with ganglionic eminence and ventricular/subventricular zone will display distinct tangential and radial cortical trajectories respectively, consistent with reports of distinct migratory streams of neurons originating therein (Fig. 1) (Letinic et al., 2002).

Materials and methods

Fetal brain specimens

This study was performed using three fixed post-mortem whole brain specimens from the tissue collection at the Department of Neurobiology at Yale University School of Medicine, which form a part of the BrainSpan Consortium collection (http://www.brainspan.org). Each specimen was assessed by a perinatal neuropathologist: no developmental abnormalities were reported. Samples were immersion fixed for 24 h and stored in 4% periodate–lysine–paraformaldehyde in 0.1 M phosphate buffer (PLP). Two specimens remained in cranio (Table 1). For scanning, in cranio samples in PLP were vacuum-sealed in polyethylene bags to maximize proximity to the radiofrequency coil elements. The bagged samples were surrounded by PLP to avoid any artifacts caused by the air-tissue interface. The ex cranio sample was surrounded by 1% agarose inside a glass tube to protect the delicate tissue from tearing which could have occurred if suspended in a liquid medium.

Scan parameters

All images were acquired using a Siemens 3 T Trio scanner using a custom-built, single channel, 2-turn solenoid coil (6.86 cm inner diameter, 11.68 cm length) (Fig. S1) with a transmit/receive switch to forgo the use of a birdcage. The solenoid design minimizes the distance between the copper turns of the coil and the sample, yielding higher signal-to-noise ratio with each turn, and improved signal uniformity compared with a phased array receive coil design. Specimens were secured with padding in the coil to minimize motion artifact produced by vibration during gradient switches. In each case, structural data were acquired using a multi-echo flash sequence (TR = 25 ms, $\alpha = 10°, 20°, 30°, 40°, 50°, 60°$; 6 echoes, TE =2.93 ms, 5.83 ms, 8.93 ms, 12.23 ms, 15.73 ms, 19.43 ms; 500 μm isotropic resolution.) (Figs. 2A–C). Diffusion-weighted data were acquired over two averages using a steady state free precession sequence (TR = 24.82 ms, $\alpha = 60°$; TE = 18.76 ms; 400 μm isotropic resolution.). Diffusion weighting was isotropically distributed along 44 directions ($b = 730$ s/mm^2) with 4 $b = 0$ images. Total scan time for the diffusion acquisitions was 6 h 34 min for the 19 pcw and 21 pcw specimens, and 10 h 50 min for 22 pcw specimen. Scan time for the multi-echo flash structural acquisition was 6 min 53 s per flip angle.

Table 1
Subject demographics.

ID	Sex	Age (pcw)	PMI (h)	Fixation time (days)	Brain state
19pcw	M	19	<21	3–5	In cranio
21pcw	M	21	<21	3–5	Ex cranio
22pcw	F	22	<21	3–5	In cranio

Table 1 gives an overview of the subjects from whom whole brain samples were obtained and scanned. pcw: post-conceptual weeks; PMI: post-mortem interval (hours); SI: scan interval (days).

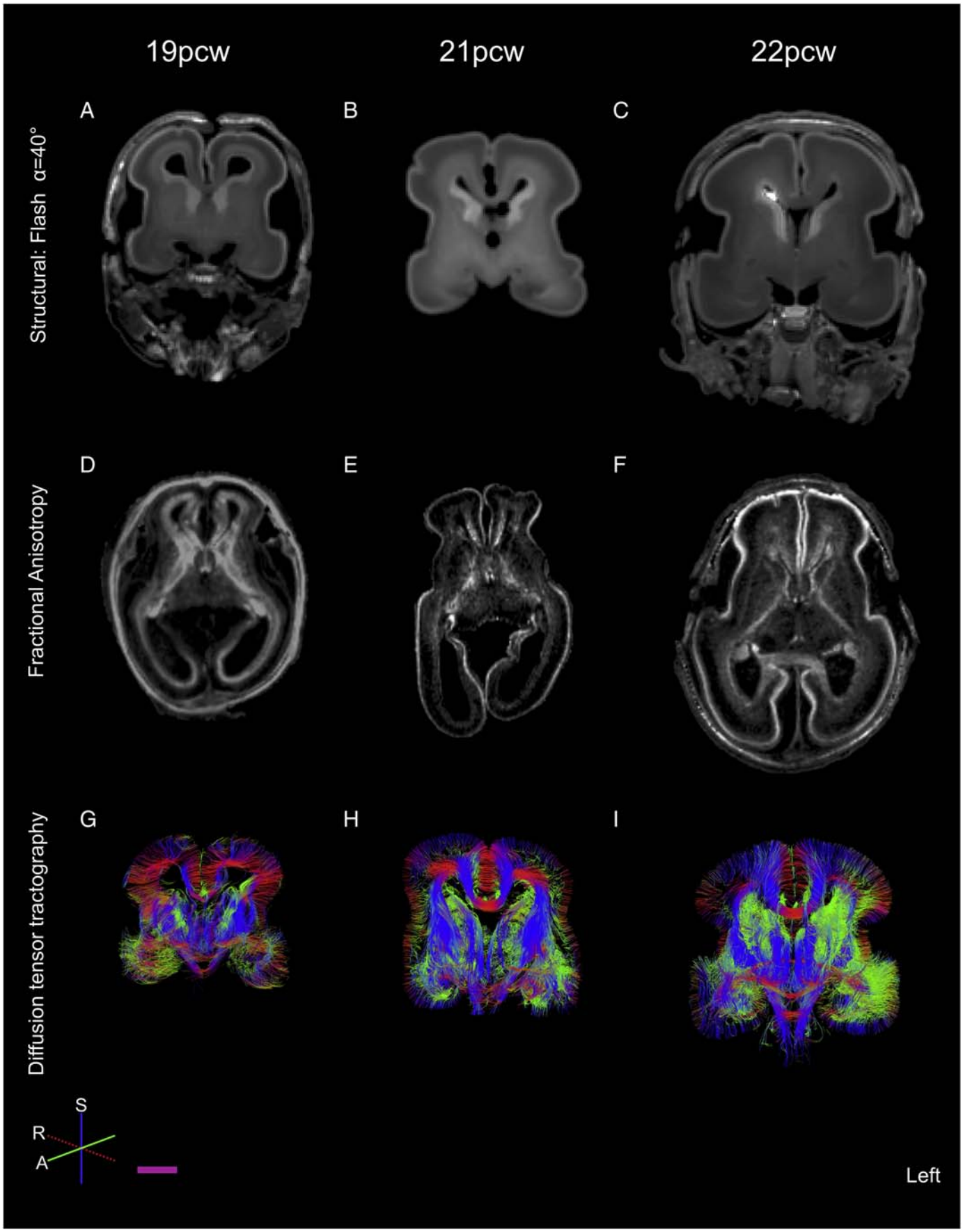
Structural MRI analysis

All structural MRI analysis was undertaken in FreeSurfer (FreeSurfer Image Analysis Suite, Massachusetts General Hospital, Charlestown, MA; http://www.freesurfer.net). Structural images were manually reoriented to a standard RAS (Right Anterior Superior) orientation. The two transient proliferative zones of interest: ganglionic eminence and dorsopallial ventricular/subventricular zone, were assessed across the range of structural images acquired in the multi-echo flash sequence; images acquired at $\alpha = 40°$ provided optimal subcortical contrast (Figs. 3A–D). The structures of interest were manually masked with reference to developmental neuroanatomy atlases (Bayer and Altman, 2007; Griffiths et al., 2010) and previously accepted definitions from MRI and histological studies (Radoš et al., 2006) (Fig. 3). The ganglionic eminence was masked in its entirety, from the rostral extremity of the anterior horn of the lateral ventricle, excluding to extension of the rostral migratory stream, along the lateral border of the lateral ventricle to hippocampus (Fig. 3E). At the gestational ages studied here, the medial and lateral components of the ganglionic eminence were no longer distinguishable from one another. The pallial ventricular/subventricular zone was masked rostrally from the anterior extremity of the anterior horn of the lateral ventricle, and caudally to the level of the posterior extremity of GE (Fig. 3F). Anatomical masks were resampled into the diffusion space using rigid body registration (FSL Linear Registration Tool: FLIRT) (Smith et al., 2004; Woolrich et al., 2009).

Diffusion-weighted MRI analysis

All diffusion-weighted MRI analysis was undertaken using the Diffusion Toolkit and Trackvis (Wang et al., 2007; http://trackvis.org). Raw data were reconstructed using a diffusion tensor imaging model (DTI), yielding maps of fractional anisotropy (FA) (Figs. 2D–F). A DTI pathway tracking algorithm was subsequently used to undertake deterministic tractography across the entirety of each brain specimen (second order Runge–Kutta method; step length = 0.5). Pathways were terminated when the angle between two successive orientation vectors exceeded 45°, an angle threshold which was not overly constrictive for this exploratory analysis of the fetal brain, particularly given the more variable factors underlying diffusion anisotropy compared to the

Fig. 2. Overview of magnetic resonance imaging data acquired from post-mortem, formalin-fixed human fetal brain samples. Structural data were acquired for each sample using a multi-echo flash sequence with images acquired at $\alpha = 40°$ providing optimal contrast to identify cortical and subcortical structures of interest (A–C). Diffusion-weighted MRI was acquired for each sample using a steady state free precession sequence ($b = 730$ s/mm^2; 44 directions), yielding maps of fractional anisotropy (D–F). A diffusion tensor imaging streamline tracking algorithm was used to undertake whole-brain deterministic tractography (G–I: represent visualization of tractography output data applying a coronal slice filter). RGB directional key for tractography data (bottom left): R — right, A — anterior, S — superior. Scale bar (pink): 10 mm. pcw: post-conceptual weeks.


19pcw
21pcw
22pcw
A
B
C
Structural: Flash α=40°
D
E
F
Fractional Anisotropy
G
H
I
Diffusion tensor tractography
S
R
A
Left

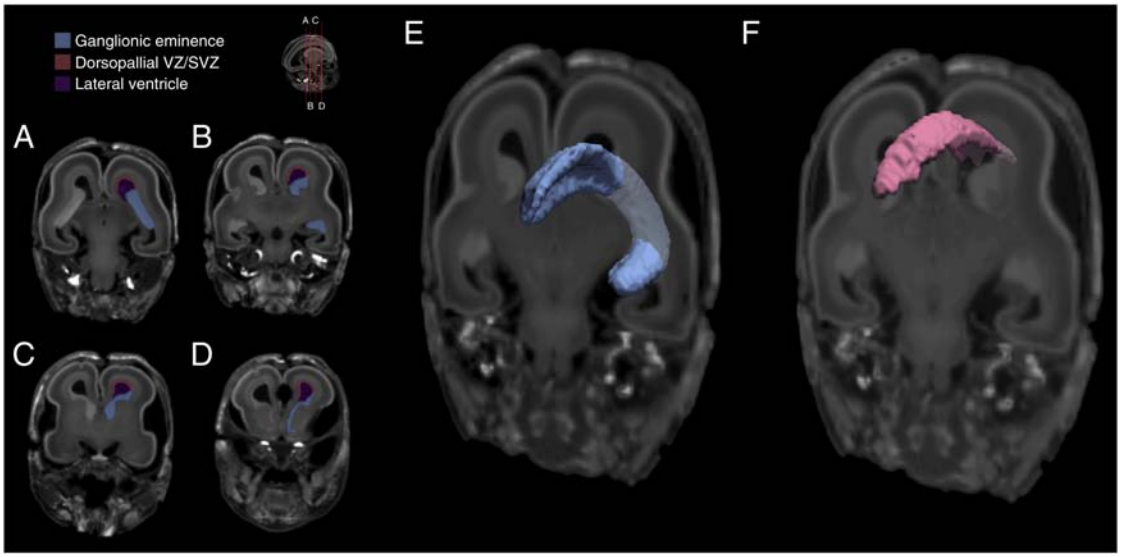


Fig. 3. Structural MRI overview of the anatomical structures of interest: subpallial ganglionic eminence and dorsopallial ventricular zone. Structural sequences acquired at $\alpha = 40°$ provide optimal contrast to define anatomical structures of interest. Ganglionic eminence (blue) was masked in its entirety, from hippocampus, in an arc along the lateral border of the lateral ventricle (A–C) to the anterior extremity of the anterior horn of the lateral ventricle (D). The anatomical masks of ganglionic eminence used in further analysis excluded the extension of the rostral migratory stream (E). Dorsopallial ventricular zone/subventricular zone (pink) was masked caudally from the level of the posterior extremity of ganglionic eminence and rostrally to the anterior extremity of the anterior horn of the lateral ventricle (A–D, F). The occipital and temporal components of VZ/SVZ are not easily demarcated anatomically, and were excluded from this study, which focused principally on frontal lobe development. VZ: ventricular zone; SVZ: subventricular zone.

adult. A binary brain mask was used to terminate tracts extending beyond brain tissue, as reported previously (Takahashi et al., 2012; Wedeen et al., 2008). The resulting whole-brain tractography outputs were passed through a spline filter and transformed to a standard RAS orientation (Figs. 2G–I).

Masks of the GE and VZ resampled into the diffusion space formed the anatomical basis for tractography analysis. Anatomical masks were used to reveal only diffusion pathways originating in each specific structure. In each case, the mask of the other anatomical region of interest was used as a pathway exclusion mask to rule out pathways associated with both structures of interest. The pathways passing through or originating in each ROI were manually divided into those with cortical or subcortical trajectories. All tractography outputs are colored for directionality at every segment using a standard RGB color map.

Results

We report our assessment of diffusion tractography pathways and their trajectories. These pathways reflect the pattern of diffusion coherence associated with the dorsopallial ventricular/subventricular zone and subpallial ganglionic eminence in the human fetal brain. References to radial coherence refer to pathways running across the cerebral mantle, perpendicular to the cortical surface, whereas references to tangential coherence refer to pathways running parallel to the ventricular or cortical surface, as defined previously (Takahashi et al., 2012).

Global patterns of FA, tractography, and structural images

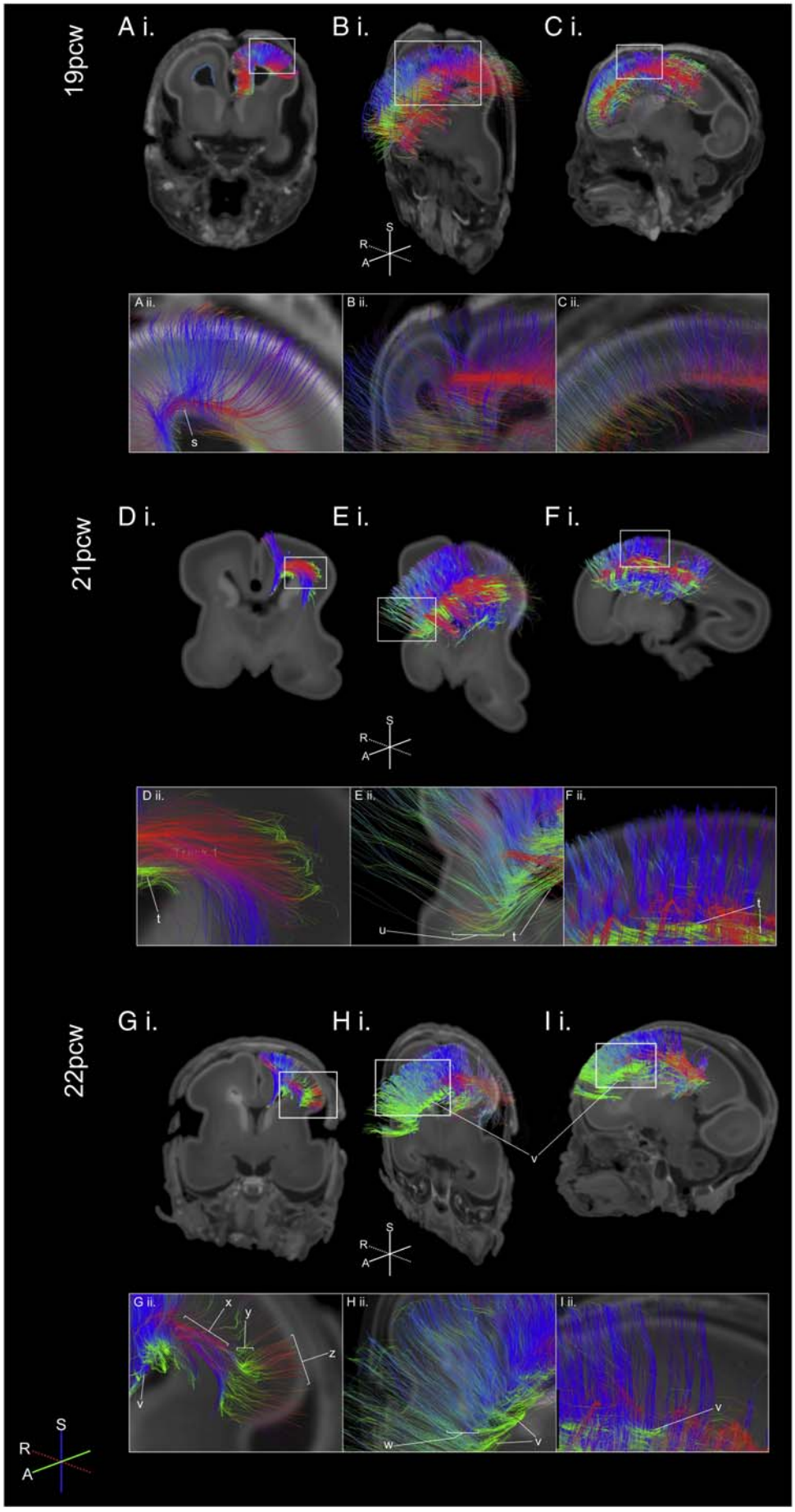
Diffusion parameter maps of FA, as well as structural images, showed consistent contrast across the three specimens under study. Assessment of the FA maps showed consistent high FA in the inner-most and outer-most cortical layers, with low FA in the middle layer (Figs. 2D–F). The general directionality and pattern in tractography pathways were also qualitatively consistent across the specimens (Figs. 2G–I). Across all three specimens structural images showed high signal intensity in the inner-most and outer-most layers, with the middle layer showing low signal intensity, corresponding broadly to layers observed on the FA maps (Figs. 2A–C).

Dorsopallial ventricular/subventricular zone: radial coherence in cortical pathways

Using anatomical masks of the dorsopallial ventricular/subventricular zone (Fig. 3), a clear dominant radial coherence was noted running from VZ, coursing through the intermediate zone (IZ) and subplate (SP) to the cortical plate (CP) at all post-conceptual ages under study (Fig. 4).

Pathways running within the VZ/SVZ itself showed a coherence running in parallel to the ventricular/subventricular border (tangential coherence), a pattern that persisted across all three samples under study (Fig. 4: s, t, v). At 19 pcw, this pattern was observed in the coronal plane (Fig. 4: s). At 21 and 22 pcw, the same pattern of tangential coherence was observed parallel to the ventricular/

Fig. 4. Pattern of radial diffusion coherence in pathways originating from dorsopallial ventricular zone/subventricular zone. Tractography pathways originating in anatomically defined dorsopallial ventricular zone (example Ai: blue) at 19, 21 and 22 pcw. A clear pattern of radial diffusion coherence is observed in pathways with a cortical trajectory, running through intermediate zone and subplate in a plane perpendicular to the orientation of the cortical surface (A, D, G). This pattern is visible along the length of the VZ/SVZ structure (C, F, I). Deviations from patterns of strictly radial diffusion coherence are observed. Within the structure of VZ/SVZ, a pattern of diffusion coherence is observed in parallel to the border of lateral ventricle (a, b, d) in the coronal plane. At 19 pcw this tangential coherence was observed in the coronal plane (a), whereas at 21 and 22 pcw, a clear pattern of diffusion coherence is visible within the VZ/SVZ in the sagittal plane (b, d) where pathways initially follow a trajectory along the A–P axis of the ventricular zone, before a clear transition to a radial coherence pattern with a cortical trajectory (c, e). A further deviation from strictly radial patterns of diffusion coherence associated with VZ/SVZ is observed in the intermediate zone at 22 pcw. Diffusion pathways originating initially in VZ/SVZ follow a radial cortical trajectory (f: red), before assuming a tangential pattern in the A–P axis through the intermediate zone (g: green), and then revert back to a radial coherence pattern before coursing into subplate and cortical plate (h: red). RGB directional key for tractography data (bottom left): R — right, A — anterior, S — superior. pcw: post-conceptual weeks.


19pcw
A i.
B i.
C i.
S
R
A
A ii.
B ii.
C ii.
s
21pcw
D i.
E i.
F i.
S
R
A
D ii.
E ii.
F ii.
t
u
t
t
22pcw
G i.
H i.
I i.
v
S
R
A
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x
y
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H ii.
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A

subventricular border, but in the antero-posterior axis. Within the VZ/SVZ pathways initially run tangential to the ventricular/subventricular border (Fig. 4: t, v) before turning to a radial trajectory coursing towards cortical plate (Fig. 4: u, w).

Interestingly, at 22 pcw diffusion pathways originating in VZ/SVZ showed a deviation from a strictly radial pattern of diffusion coherence. These pathways first follow a radial trajectory after exiting the VZ/SVZ (Fig. 4 GII-x), but then assume a tangential trajectory in the intermediate zone (Fig. 4GII-y), before reassuming a radial pattern when entering SP towards the CP (Fig. 4GII-z).

These tractography data demonstrate a clear and expected radial coherence of pathways originating within the dorsopallial ventricular/subventricular zone as they course towards the CP. However, they also show more subtle patterns of tangential diffusion coherence in these pathways, which raises the possibility that deviations may exist from the strictly radial model of migration reported previously between VZ and CP (Rakic, 1988; Takahashi et al., 2012; Xu et al., 2012).

Ganglionic eminence: tangentio-radial coherence in cortical pathways

Diffusion coherence associated with the ganglionic eminence (GE) showed a characteristic pattern of tangential followed by radial pathway directionality across all three post-conceptual ages (Fig. 5). Within the structure of the GE itself (Fig. 3E) a clear pattern of diffusion tangential to the cortical surface was evident (Fig. 5: q, r, s), extending throughout the entirety of the masked structure. The coherent tangential pathways within the GE were sharply punctuated by pathways emanating from the GE structure that assumed a radial pathway perpendicular to the cortical surface (Fig. 5: t, u, v). Interestingly, the radial pathways emanating from the GE were continuous with pathways running tangential to the cortical surface within the GE (Fig. 5: w, x, z). A tangentio-radial transition in the trajectory of pathways originating in the GE was observed at all post-conceptual ages assessed: pathways with a tangential trajectory within the GE consistently demonstrated a clearly demarcated shift to a radial trajectory before coursing through the IZ, SP and towards CP (example: Fig. 5Fii).

The position of this tangentio-radial transition in the tractography pathways and the directionality of the radial component of the tractography pathways differed at the three post-conceptual ages. At 19 pcw, radial pathways emanating from the initially tangential tractography coherence of the GE displayed a lateral and inferior trajectory towards CP (Fig. 5Bi: t), with an even distribution along the caudo-rostral axis (Fig. 5Ai: t). At 21 pcw, radial pathways took a more medial trajectory towards CP, with a regression of tracts extending from the GE in caudal regions (Figs. 5E/F). At 22 pcw, the tangentio-radial transition yielded pathways whose radial component had a predominantly mediodorsal trajectory with a clear dominance in the rostral GE (Fig. 5H/I).

These tractography data reveal tangential diffusion coherence within the GE, with a clear tangentio-radial transition in the diffusion pathways as they emerge from the GE and course across IZ and SP towards CP. The tangentio-radial transition yielding radial directionality towards CP appears to regress in a caudo-rostral direction across the short period of fetal development under study (Figs. 5C, I, F: arrow heads), as well as a lateral-inferior to medial dorsal predominance consistent with previous literature (Takahashi et al., 2012).

Discussion

The primary aim of this study was to assess patterns of diffusion coherence associated with subpallial ganglionic eminence (GE) and dorsopallial ventricular/subventricular zone (VZ): transient embryonic regions of neuroproliferation. We have used a combination of post-mortem diffusion-weighted and structural MRI to demonstrate the presence of two clear and distinct three-dimensional patterns of diffusion coherence associated with these structures in the human fetal brain: a radial pattern originating in VZ, and a tangentio-radial pattern originating in GE. The assessment of these complex patterns in the human fetal brain provides a unique three-dimensional insight into the structural complexity underlying neurodevelopment and the migratory events and structures involved in corticogenesis.

Diffusion coherence in the fetal brain

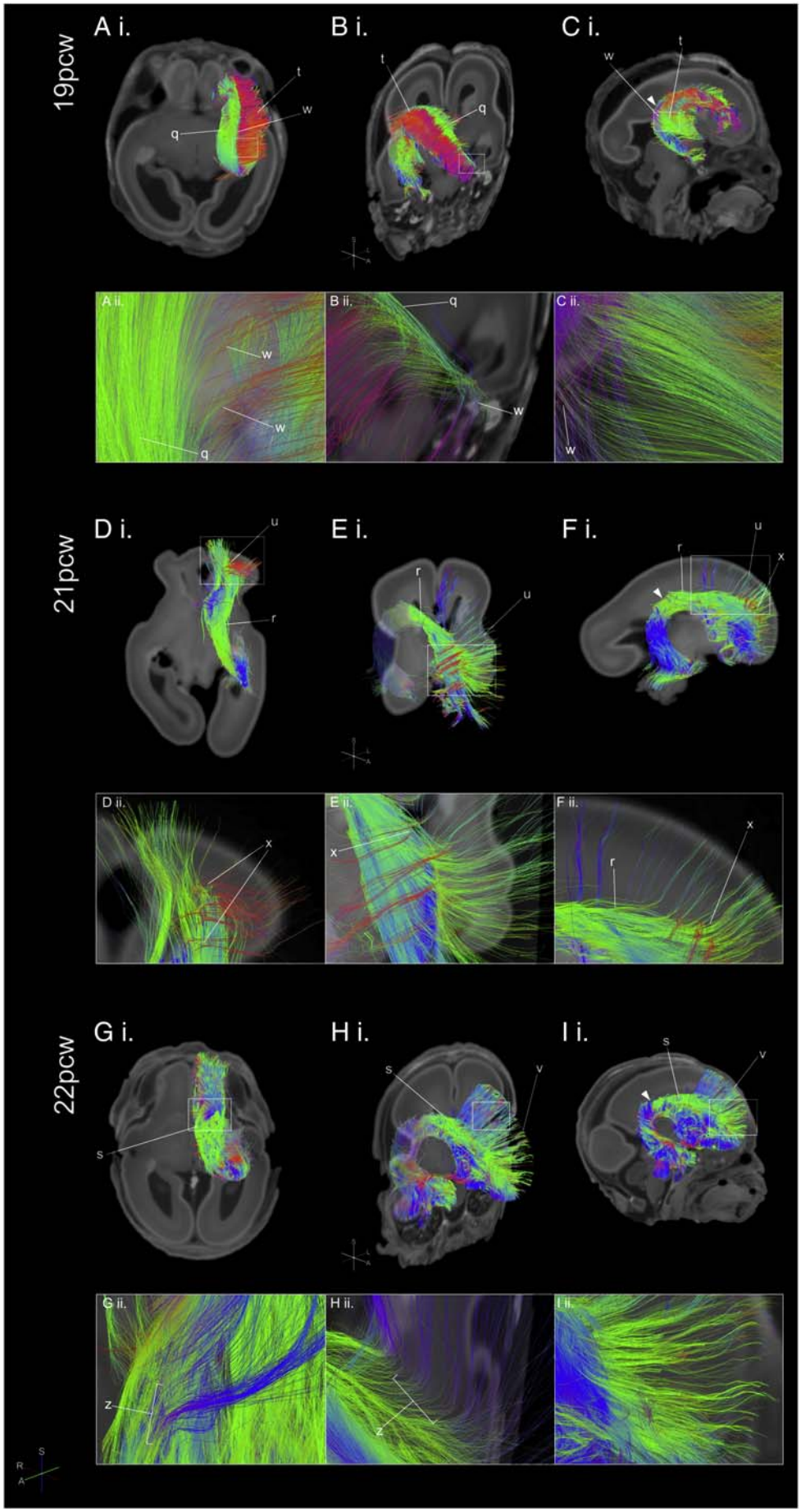
While an increasing number of tractography studies are published in the literature, there is surprisingly little histological validation of diffusion tractography outputs, even in the adult brain. Tractography pathways are not a direct reflection of underlying tissue microstructure, but rather an indication of patterns of diffusion coherence and directionality in the underlying tissue. The fetal brain samples under study are aged 19, 21 and 22 pcw: the biological basis of diffusion anisotropy is therefore not influenced by factors reported in adults, such as myelinated white matter fiber bundles and mature long range axonal structure (Beaulieu, 2002). In the fetal brain interpretation of diffusion tractography pathways is complicated by the existence of radial glial fibers, developing vasculature, migrating neurons and other cell bodies, as well as emerging axonal structures (Xu et al., 2012). Our previous work has demonstrated that while penetrating vascular structures, migrating cells and radially orientated axons may influence patterns of diffusion coherence in the fetal brain, histological evidence suggests a dominant role for radial glial fibers as a driving force behind radial coherence patterns observed in post-mortem fetal brain tractography analysis (Xu et al., 2012).

Radial coherence and the dorsopallial ventricular zone

In the current study, we successfully dissociated two distinct diffusion pathways. The first showed a pattern of diffusion coherence originating in the dorsopallial VZ/SVZ, with a dominant radial directionality coursing towards cortical plate (Figs. 4/6). This pattern has been visualized in previous diffusion imaging studies of the brain, but here we expand on prior work to show a clear association with the dorsopallial ventricular/subventricular zone as we have been able to use anatomical information provided by concurrent high-resolution structural imaging. The radial pattern is consistent with the radial unit hypothesis of neuronal migration in the developing mammalian cortex, whereby the dorsopallial proliferative zones form an effective protomap which is translated through a complex and regulated period of inside-out neuronal migration to establish cortical structure (Rakic, 1988).

Interestingly, certain deviations from the strictly radial pattern of diffusion coherence were associated with the VZ/SVZ in this study. Such deviations were seen within the VZ/SVZ itself (Figs. 4s/t, 6) and in pathways emanating from VZ/SVZ, particularly showing directionality tangential to the cortical surface in the intermediate zone (Fig. 4x–z).

Fig. 5. Pattern of tangential diffusion coherence in pathways originating from subpallial ganglionic eminence. Tractography pathways originating in anatomically defined subpallial ganglionic eminence (Fig. 2E) at 19, 21 and 22 pcw. A clear pattern of diffusion coherence was apparent within the structure of the ganglionic eminence (a, b, c), with pathways following the arc of the structure along the wall of the lateral ventricles in all three samples under study. At all ages, pathways with a radial cortical trajectory were observed emanating from the ganglionic eminence (d, e, f); closer inspection demonstrated that the tangential pathways within the ganglionic eminence were continuous with these radial pathways, with a clear tangentio-radial transition in the overall trajectory (g, h, j). The emanating radial pathways showed variation in cortical trajectory across the age range studied. At 19 pcw radial pathways followed a lateral and inferior trajectory towards cortical plate (Bi/ii: red), which shifted more medially at 21 pcw (Ei/ii), and showed a clear mediodorsal dominance at 22 pcw (Hi/ii). Furthermore, the radial pathways showed a differing distribution along the caudo-rostral axis of the ganglionic eminence in the three brain samples under study. At 19 pcw, an even distribution of radial pathways was observed along the rostro-caudal axis of the GE (g) which showed a gradual shift regression caudally at 21 pcw (e) and a clear shift to rostral dominance at 22 pcw (f). These diffusion characteristics demonstrate a tangentio-radial pattern of diffusion coherence between the ganglionic eminence and cortical plate. RGB directional key for tractography data (bottom left): R — right, A — anterior, S — superior. pcw: post-conceptual weeks.


19pcw
A i.
B i.
C i.
t
w
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A ii.
B ii.
C ii.
21pcw
D i.
E i.
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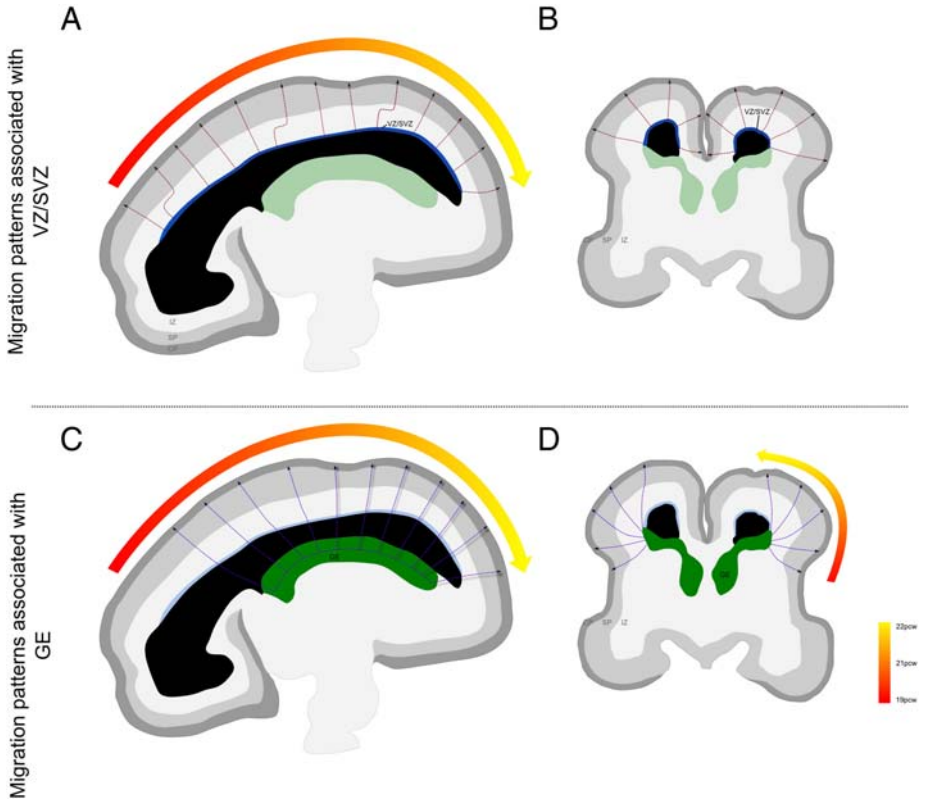

Fig. 6. Overview of observed three-dimensional patterns in diffusion coherence associated with ganglionic eminence and dorsopallial ventricular/subventricular zone. The dorsopallial ventricular/subventricular zone and the ganglionic eminence were associated with two distinct patterns of diffusion coherence. The diffusion pathways emanating from dorsopallial ventricular zone/subventricular zone show a clear dominance in radial coherence, with individual tracts predominantly assuming a pathway directly towards cortical plate. Some deviations from the strictly radial pattern were observed in the intermediate zone, where there was a deviation from a radial to tangential trajectory in the rostrocaudal axis, before a return to a radial pathway towards cortical plate (A). Within dorsopallial ventricular zone/subventricular zone itself, diffusion coherence was tangential to the cortical surface in both the sagittal and coronal views (A/B: red lines within VZ/SVZ [blue]). Diffusion coherence within ganglionic eminence (green) showed a strong directionality tangential to the cortical surface (C), with individual streamlines showing a sharply punctuated transition upon exiting the ganglionic eminence, assuming a radial pathway coursing towards cortical plate (C/D). Both patterns of diffusion coherence demonstrated a pattern of temporal regression with a caudo-rostral (A, C) and lateral-inferior to medial dorsal (D) predominance, as described previously.

This deviation from a radial pattern has been reported in histological studies of neuronal migration in the intermediate zone. O'Rourke and colleagues focally injected DiI and labeled cells migrating in all directions over long distance in the mouse brain, originating within the VZ/SVZ (O'Rourke et al., 1997). Their results reveal an extensive tangential dispersion of cortical cells mediated predominantly or exclusively via non-radial migration of post-mitotic neurons. They suggest that cortical neurons arise from a progenitor cell, and subsequently either migrate radially to form a cluster, or move tangentially at any depth within the developing cerebral wall, including the VZ, SVZ, intermediate zone and cortical plate. A similar pattern was observed in human organotypic slice culture, using analysis on a cellular level to observe migrating neuronal precursors, showing that "GABA-ergic neurons [originating in VZ/SVZ] migrate in non-radial, neurophilic fashion within the VZ/SVZ but switch to a radial, gliophilic mode in the IZ, after exiting the VZ/SVZ" (Letinic et al., 2002).

Our data are in clear agreement with these histological studies, demonstrating patterns of tractography coherence tangential to the cortical surface observed within the SVZ/VZ, and a clear shift to a radial trajectory upon exiting the VZ/SVZ and with some deviations from radial directionality in layers other than cortical plate, such as the IZ.

Tangentio-radial coherence and the subpallial ganglionic eminence

Patterns of diffusion coherence associated with GE showed a clear contrast to that observed in dorsopallial VZ/SVZ. Most prominently, the diffusion coherence within GE showed a dominant directionality tangential to the cortical surface in the sagittal plane (Figs. 5/6), within a clear tangentio-radial transition in these continuous pathways as they emerged from the GE, yielding pathways which course radially through the cerebral mantle to the cortical plate.

The pattern of tangential migration in the GE is well supported by histological data (Yokota et al., 2007) and thought to be crucial to the migration of cortical interneurons to specific locations. A recent study applied *in vivo* two-photon microscopy to visualize the dynamics of migration in corticogenesis as neuronal cells migrated away from the GE (Yokota et al., 2007). In keeping with our observation of a sharp transition between tangential and radial diffusion coherence at the border of the GE, this cellular imaging approach showed a multidirectional movement of interneurons once they invade the cortex from their origins in the GE. This pattern was thought to be stimulated by local cues influencing the distribution of interneurons to different cortical areas. The dependence of the tangential and radial migration of interneurons on different mechanisms has since been confirmed by studies applying RNA interference (RNAi) techniques to the developing rat brain (Elias et al., 2010). Short hairpin RNA (shRNA) knock-down of connexin-43 (Cx-43), a key component of gap-junction adhesion complexes, showed that while a reduction in Cx-43 during development does not disturb tangential migration patterns, it plays a crucial role in the switch to radial migration and the direction of interneurons to their appropriate laminar position. The tangential and radial components of interneuron migration show a clear mechanistic separation at a cellular level, which we are potentially able to observe through distinct changes in diffusion coherence patterns visualized in this study with diffusion MRI.

Complex migratory streams and disease

The observation that patterns associated with neuronal migration during human development can be visualized through a non-invasive imaging modality such as diffusion MRI is of potential future interest in the investigation of neurodevelopmental pathology. The anatomical structures of interest in this study are particularly susceptible to hypoxic injury in premature neonates (Volpe, 2009). A recent post-mortem study of neonates with periventricular prematurity associated hemorrhage (PAH) showed a marked suppression of cellular proliferation in the ganglionic eminence, potentially explaining the reduced brain volume and cognitive deficits often seen in survivors of PAH. Many diseases of adulthood are also increasingly associated with aberrancies in neuronal migration during fetal corticogenesis (Brandon and Sawa, 2011; Kamiya et al., 2012; Steinecke et al., 2012). An ability to assess the developing fetal brain in vivo with diffusion MRI could allow us to probe the differences in diffusion coherence associated with neuroproliferative anatomical structures and potentially infer the dysfunction in neuronal migration which may underlie many developmental or psychiatric disorders.

While fetal MRI is playing an increasing role clinically in prenatal care and monitoring (Pooh and Pooh, 2008; Shekdar and Feygin, 2011), the application of complex diffusion-weighted or structural MRI modalities in utero has been limited by issues such as fetal motion artifact and the short acquisition time available (Prayer, 2011). The use of these techniques for *in vivo* studies of human neurodevelopment can therefore not yield data of comparable quality to that acquired *ex vivo* in this study. However the data presented here emphasize the need for robust and fast in utero sequences to acquire data during development and potentially follow-up with longitudinal studies beginning during pregnancy and continuing postnatally.

Limitations of the study

This study involved the assessment of a small, but unique cohort of post-mortem human fetal brains. While the small sample size is a clear limitation of the study, given the nature of the samples and the obvious difficulties in acquiring such samples post-mortem, there is clear value in undertaking complex analysis, even over three closely spaced time points. While the samples were obtained from medically indicated clinical procedures and were assessed by a perinatal neuropathologist to rule out underlying neurodevelopmental abnormalities, it remains possible that some aberrancies existed but were undetected.

Diffusion pathways presented in this study are derived from a diffusion tensor imaging deterministic tractography approach. Traditionally this tracking approach has low sensitivity for crossing fibers. Therefore it remains possible that the radial and tangential components of the pathways reported here represent distinct structures which may artifactually appear to be continuous due to the limited ability of DTI to resolve crossing fibers. However this explanation is unlikely for a number of reasons. Firstly, this dataset was acquired *ex vivo* at an isotropic resolution of 400 μm, significantly higher than those acquired *in vivo*, therefore if two distinct structures did exist, at least some streamlines would have a trajectory suggesting this. Secondly, data from cellular studies suggest that migration patterns shift as neurons exit proliferative zones (O'Rourke et al., 1997), the point at which a sharp angle is often observed in the tractography pathways in this study. Finally, radial glial fiber orientation plays a dominant role in diffusion anisotropy in the fetal brain rather than long-range white matter bundles at 19–22 pcw (Xu et al., 2012); the kind of complex organized crossing fiber structure which could cause such artifactual 'collision' of radial and tangential streamlines in DTI tractography data has not been described histologically in the fetal brain. Moreover, in an exploratory study to image such poorly characterized structures, the limitation of DTI would be comparable, if opposite, to the limitation of HARDI: DTI may artifactually connect distinct structures, but HARDI may artifactually disconnect continuous structures.

Conclusion

This study demonstrates two distinct patterns of diffusion coherence associated with two major neuroproliferative structures in the human fetal brain using a combination of post-mortem high-resolution diffusion-weighted and structural MRI. The observed radial pattern associated with dorsopallial ventricular/subventricular zone, and the tangentio-radial pattern associated with subpallial ganglionic eminence are consistent with reports of neuronal migration pathways identified during human corticogenesis, supported by our prior studies of comparative fetal diffusion MRI and histology. The ability to visualize both dominant and subtle migratory structures in three-dimensions offers a unique insight into complex neurodevelopmental processes beyond the traditional view offered by histology. Our data provide a further proof of principle that fetal MRI is a potentially useful modality in understanding normal human development and various disease processes whose etiology may originate in aberrant fetal neuronal migration. There is a clear need to invest resources in developing MRI sequences to face the unique challenges of in utero imaging, such that high-quality diffusion MRI acquisitions could be obtained during human gestation.

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The data acquired in this study form a part of the BrainSpan Atlas of the Developing Human Brain. This is a unique resource for studying human brain development, providing a broad and detailed anatomical analysis of gene expression across human brain development, comprising ISH, RNA sequencing and microarray data, along with supporting neuroanatomical reference content. The BrainSpan data is accessible via the Allen Brain Atlas data portal http://www.brain-map.org or directly at http://www.developinghumanbrain.org or http://www.brainspan.org.

Conflict of Interest

None.

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