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Dorsal and ventral pathways in language development

Jens Brauer ^{a,*}, Alfred Anwander ^a, Daniela Perani ^b & Angela D. Friederici ^a

^a Max Planck Institute for Human Cognitive and Brain Sciences, Department of Neuropsychology, Leipzig, Germany

^b Vita-Salute San Raffaele University, Division of Neuroscience IRCCS San Raffaele, Milano, Italy

Research Report

* Address for Correspondence:

Jens Brauer

Max Planck Institute for Human Cognitive and Brain Sciences

Department of Neuropsychology,

Stephanstrasse 1a,

04103 Leipzig, Germany

<http://www.cbs.mpg.de/~brauer>

Abstract

The dorsal and ventral information streams between inferior frontal and temporal language regions in the human brain are implemented by two fiber connections that consist of separable tracts. We compared the maturation of the two connections including their subcomponents in three different age groups: newborn infants, 7-year-old children, and adults. Our results reveal a maturational primacy of the ventral connection in the language network associating the temporal areas to the inferior frontal gyrus during early development, which is already in place at birth. Likewise, a dorsal pathway from the temporal cortex to the premotor cortex is observable at this early age. This is in contrast to the dorsal pathway to the inferior frontal gyrus which matures at later stages in development and might play a role in more complex language functions.

Keywords

Dorsal and ventral pathways, Development, DWI, Inferior fronto-occipital fasciculus, Arcuate fasciculus, IFG

1 Introduction

One hundred and fifty years ago the seminal work of the French physician and anthropologist Paul Broca provided an important insight into the brain basis of the human faculty of language (Broca, 1865). One of his patients suffering from a severe aphasia was only able to pronounce the sole syllable *tan* although his understanding of language was apparently intact. Even when he tried to speak full sentences with his voice following a sentential melody, his utterance was nothing but a stream of *tans*. After this patient passed away, Broca investigated his brain *ex vivo* and observed a lesion in the left inferior frontal gyrus (IFG), an area that became known as Broca's area.

Only a few years later, the German neurologist Carl Wernicke described the role of lesions to the superior temporal gyrus (STG) in aphasia as derived from the symptom patterns of his patients (Wernicke, 1874). In his work, Wernicke suggested separating motor (expressive) aphasia, occurring as a result of a lesion to the IFG, from sensory (receptive) aphasia, as a result of a lesion to the posterior part of the STG, later on labeled as Wernicke's area. He also assumed a third type of aphasia, conduction aphasia, as a result of a lesion to the connection between the sensory and the motor part of the language system, although not much was known about how this connection was implemented in the brain. This idea was taken up and elaborated by Ludwig Lichtheim (1885). Wernicke thought of this connection to be formed and sustained during language acquisition and development as an important process to achieve mature language abilities.

Adapted over time and generalized beyond aphasia, the Broca-Wernicke-Lichtheim model of language implementation in the brain became the most influential model used by generations of neuroscientists to address issues of typical and atypical language processing and its central assumptions still provide a very useful framework (Poeppel & Hickok, 2004). Current progress in the field of neuroscience of language has provided a number of technologies for data acquisition and data processing. Today, the structural and functional neuroanatomy of the brain basis of language is accessible *in vivo*, and there is a consensus that Wernicke was correct in his assumption of a direct connection between the frontal and temporal language centers. For a long time, textbook knowledge was that a dorsal connection via the arcuate fasciculus (AF) or part of the superior longitudinal fasciculus (SLF) was the

anatomical realization of this association. However, more recent work has rediscovered the importance of an independent second connection between the two language centers that probably fulfills an important role within the network (Brauer et al., 2011; Frey et al., 2008; Friederici et al., 2006; Parker et al., 2005). This connection is ventrally located, running through the extreme capsule (EmC) and external capsule (EC) via the inferior fronto-occipital fasciculus (IFOF), sometimes also named extreme capsule fiber system (ECFS) (Catani, 2009; Frey et al., 2008; Friederici, 2011; Makris & Pandya, 2009; Saur et al., 2008). For a comprehensive overview on the ventral pathway's history, see Weiller et al. (2011).

The dorsal and ventral information streams are assumed to each consist of several fiber bundles (Friederici, 2009). The AF and part of the SLF have been proposed to form the dorsal connection (Brauer et al., 2011; Frey et al., 2008; Saur et al., 2008). The AF connects superior temporal (Brodmann area (BA) 41, 42) and middle temporal regions (BA 21, 22, 37) to different parts of the prefrontal cortex, namely to the IFG (BA 44, 45), the middle frontal gyrus (MFG) (BA 6, 8, 9) and the precentral gyrus (PCG) (Catan et al., 2002; Catani et al., 2005; Thiebaut de Schotten et al., 2012). In addition to the AF, there is the SLF, which contains three separable bundles connecting the parietal cortex to the prefrontal cortex (SLF I, II and III, Makris et al., 2005). SLF III connects the inferior parietal lobe with BA 44 in Broca's area and to BA 6. The other components of the SLF (SLF I and SLF II) are functionally less language-specific and do not connect to Broca's area but rather to BA 6, 8, 9, 32 (SLF I) and BA 6, 8, 9 and 46 (SLF II) (Makris et al., 2005 and Thiebaut de Schotten et al., 2012).

For the ventral connection at least two bundles have been proposed, the IFOF and the uncinate fasciculus (UF). The IFOF runs through the EmC/EC and connects occipital, medial parietal, and posterior temporal areas to frontal areas (Catani et al., 2002; Martino et al., 2010; Thiebaut de Schotten et al., 2012). *Ex vivo* fiber dissection of the IFOF proposed that this bundle actually hosts two subcomponents, a superficial tract (V1) and a deep tract (V2) (Martino et al., 2010 and Sarubbo et al., 2011). The superficial tract (V1) was proposed to be involved in the language network terminating in the pars triangularis (BA 45) and pars orbitalis of the IFG, while the deep tract (V2) terminates in three frontal regions: An anterior component in the frontal pole and orbitofrontal cortex (OFC), a middle component in the middle

frontal gyrus (MFG), and a posterior component in the MFG and dorsolateral prefrontal cortex (DLPFC) (Sarubbo et al., 2011). While the deep tract (V2) of the IFOF probably mainly passes through the EC, the superficial tract (V1) of the IFOF covers a more lateral part of the capsules and runs through the EmC and EC (Martino et al., 2010). The two capsules are very narrow structures separated by the claustrum that forms a thin layer of gray matter. Current image resolution in diffusion-weighted imaging (DWI) is not sufficient to clearly separate EC and EmC fibers in diffusion data. The UF was also shown to be relevant for language processing (Friederici et al., 2006 and Papagno, 2011). It connects the anterior temporal lobe and the temporal pole (BA 38) to the orbitofrontal cortex (BA 10, 11, 47) and the ventro-medial located frontal operculum (Thiebaut de Schotten et al., 2012). The UF runs laterally and ventrally to the fibers of the IFOF through the EmC (Martino et al., 2010).

In terms of the neuroanatomical development of the language network during early ontogeny DWI data suggest that newborn infants do not yet possess a fully matured dorsal connection from the STS/STG to the language region in the IFG (Perani et al., 2011). Rather, the newborns' dorsal connection terminates in the premotor cortex (PMC). These two different termination points of the dorsal connection, one terminating in the PMC (dorsal pathway D1), one terminating in BA 44 in Broca's area (dorsal pathway D2), respectively, have been proposed to form two distinct pathways of the dorsal connection (Friederici, 2011 and Friederici, 2012). Dorsal pathway D1 connecting to the PMC is already observable at birth (Perani et al., 2011) and potentially responsible for sensory-to-motor mapping (Saur et al., 2008), a function that is in place very early in language learning (Gervain et al., 2008, Perani et al., 2011 and Teinonen et al., 2009). Dorsal pathway D2 connecting to BA 44 in the IFG is not yet observable by DWI in newborns. This subcomponent of the dorsal connection is probably responsible for the ability to process complex sentence structures as observed in adults' common activation of BA 44 and STS/STG during sentence processing of more complex types (Bornkessel et al., 2005 and Friederici et al., 2009). It is unknown how the two pathways of the dorsal connection that terminate in the PMC (D1) and in the IFG (D2) mature during development. However, recent findings from developmental linguistics show that the ability to process

complex sentences develops at around the age of 7 years (Dittmar et al., 2008; Hahne et al., 2004; Knoll et al., 2012).

For the current analysis, we concentrated on pathways connecting the frontal language region in the IFG to the posterior language region, i.e., the dorsal pathways D1 and D2 and the ventral pathway via the IFOF including V1 and V2. The ventral superficial tract V1 as described in the adult brain (Martino et al., 2010) is evident in newborns (Perani et al., 2011). It is unknown, however, whether the deep tract (V2) of the IFOF shows the same maturation trajectory as the superficial tract (V1). If the dorsal pathway D2 terminating in Broca's area is relevant for the processing of complex linguistic structures as described above, this connection should be in place at age 7 (Brauer et al., 2011).

In order to describe the maturation of the dorsal and the ventral pathways of the language network, we compared DWI data from previously published studies including newborn infants (Perani et al., 2011), 7-year-old children, and adults (Brauer et al., 2011). The infant data were acquired at a different institution and scanner than the child and adult data. We used fiber tracking to delineate the two pathways and their components as they have been described for the adult brain and we compared their microstructural properties using the diffusion MR biomarker of fractional anisotropy (FA). The comparison of adult data with infant and child data sheds light on the structural maturation trajectory of the human language network.

2 Materials and methods

2.1 Participants

Here we reanalyzed diffusion imaging data from Brauer et al. (2011) and Perani et al. (2011). Data from 19 newborns (age 2 days, range 1 – 3 days), 10 children (5 girls, age 7.0 years, range 5 – 8 years), and 10 adults (5 female, age 27.8 years, range 24 – 32 years) were available. All participants or the parents of non-adult participants gave written informed consent. The studies were approved by the respective local ethics committees of the University of Leipzig (Brauer et al., 2011) and San Raffaele Scientific Institute (Perani et al., 2011).

2.2 Data acquisition

Diffusion MR images from newborns were acquired on a Philips 3 Tesla Achieva scanner (Philips Medical Systems, Best, The Netherlands) using an EPI sequence with a voxel size of $1.4 \times 1.4 \times 2 \text{ mm}^3$ covering the whole brain (40 axial slices) in 21 diffusion-encoding gradient directions, b-value 1000 s/mm^2 , and one image without diffusion weighting. Motion-affected diffusion-weighted images were individually removed. This correction was necessary for one image (out of 21 diffusion-weighted images) from five individuals, for two images from four individuals, and for three images from one individual dataset. The remaining images were corrected for motion using rigid body transformations (Jenkinson et al., 2002). The motion correction was combined with a co-registration to a newborn reference brain and resampled to an isotropic resolution of 1 mm. As reference brain, the most typical brain was selected out of the group by nonlinear warping of every brain on all other brains and quantifying the similarity. This brain was then aligned with the Talairach coordinate system (Talairach & Tournoux, 1988).

Diffusion MR images from children and adults were acquired on a 3 Tesla MR scanner (TRIO 3T, Siemens Healthcare, Erlangen, Germany) with a refocused spin echo-planar-imaging sequence (Reese et al., 2003), TE 100 ms, TR 12 s, providing 60 diffusion-encoding gradient directions with a b-value of 1000 s/mm^2 , voxel size 1.7 mm^3 isotropic, matrix 128×128 , FOV $220 \times 220 \text{ mm}^2$.

Seven images without diffusion-weighting were obtained at the beginning of the scanning sequence and after each block of 10 diffusion-weighted images as anatomical reference for offline motion correction. Interleaved measurement of 72 axial slices with 1.7 mm thickness (no gap) covered the entire brain. Random noise in the data was reduced by averaging three acquisitions. Additionally, fat saturation was employed together with 6/8 partial Fourier imaging, Hanning window filtering and parallel acquisition (generalized auto-calibrating partially parallel acquisitions, GRAPPA (Griswold et al., 2002), with acceleration factor 2). Twenty-one images without diffusion weighting were used to estimate motion correction parameters with the same algorithm as was used for the newborns. The motion correction was combined with a global registration to the structural scan of the same participant which was aligned with the Talairach coordinate system and resampled to an isotropic resolution of 1 mm. Finally, for each voxel of all participants in each of the

three groups, a diffusion tensor was fitted to the data, and FA was computed (Basser et al., 1994).

2.3 Fiber tracking

Anatomical connectivity and fiber orientation in brain white matter was investigated by fiber tracking based on the diffusion tensor maps (Anwander et al., 2007; Conturo et al., 1999). Mean DTI data averaged for each group were examined by a whole brain deterministic fiber tracking. Therefore, the preprocessed diffusion images for each group were aligned to a template brain by nonlinear registration (Thirion, 1998) implemented in LIPSI (Lohmann et al., 2001) and averaged to one dataset. A diffusion tensor was fitted to the combined data, resulting in one averaged diffusion tensor of each voxel in each group, and FA was computed for each voxel. In this way, the averaging was integrated implicitly into the tensor fitting procedure to avoid averaging of diffusion tensors. The fiber tracking algorithm used the entire diffusion tensor to deflect the estimated streamline trajectory corresponding to the fiber tract (Lazar et al., 2003) as implemented in MedINRIA according to Fillard et al. (2007). Trajectories were started in all voxels (voxel size: 1 mm³) with a FA > 0.13 for the children and adults and FA > 0.1 for the newborn infants. We applied the same tracking procedure to all three data sets, i.e. for newborns, 7-year-old children and adults. All streamlines crossing two volumes of interest were selected as white matter connections between the two regions. Following Perani et al. (2011), we selected the streamlines connecting ventral precentral gyrus (BA6) with the temporal lobe via the dorsal route as dorsal pathway D1 and the streamlines connecting the IFG (BA44) with the temporal lobe via the dorsal route as the dorsal pathway D2. The selection of the streamlines of the ventral IFOF was done in the same way with one region-of-interest (ROI) covering the EmC and EC and a second ROI covering the posterior temporal and occipital lobe following the selection criteria proposed by Catani and Thiebaut de Schotten (2008). In a second step, we selected the superficial component of the IFOF connecting to the lateral part of the pars triangularis (BA45) following the method of Sarubbo et al. (2011). The remaining deep component V2 of the IFOF was subsequently subdivided into an orbital component connecting to the frontal pole and the orbito-frontal cortex and a dorsal component connecting to the middle and superior frontal gyrus.

2.4 Quantitative analysis

We measured FA of the diffusion tensor in the different sub-components of the fiber tracts as a microstructural biomarker of structural maturation for the different age groups. Therefore, we computed the individual FA maps for all subjects and normalized them for each group to the template brain that was used for fiber tracking. The group average FA image was skeletonized with the TBSS (Smith et al., 2006) method. All voxels of the skeleton with a mean FA value smaller than the FA threshold were removed from the skeleton. In a second step, TBSS provided for each point on the skeleton the locally maximal FA value in a small neighborhood perpendicular to the 3D skeleton and copied this value for each subject on the skeleton. For each subject and each tract, all voxels that were crossed by at least one streamline of the selected bundle were selected. In the next step, all voxels of the white matter skeleton within this volume of the fiber bundle were used to compute the mean FA values of the skeleton voxel within this tract. In this way, the mean FA value for each bundle was less influenced by partial volume effects at the borders of the fiber bundle compared to a method that uses all FA values within the bundle. In addition, the values were less influenced by the FA values at the noisier fanning endpoints of the fiber bundles. Statistical comparison indicated whether FA values differed significantly. Greenhouse-Geisser correction for degrees of freedom was applied as required (Greenhouse and Geisser, 1959).

3 Results

Fiber tracking results were compared across the three age groups: newborn infants, 7-year-old children and adults for the dorsal (D1, D2) and the ventral tracts (V1, V2). We knew that newborns only show dorsal tract D1 terminating in the premotor cortex, and not tract D2, which in adults runs further into the IFG. Adults, on the other hand show both pathways (Fig. 1A and 1C) (after Perani et al., 2011). In contrast to infants, for children we were able to track D2 connecting to the IFG (Fig. 1B, in blue), showing that 7-year-old children possess a connectivity pattern of the dorsal route that is similar to the one observed for adults.

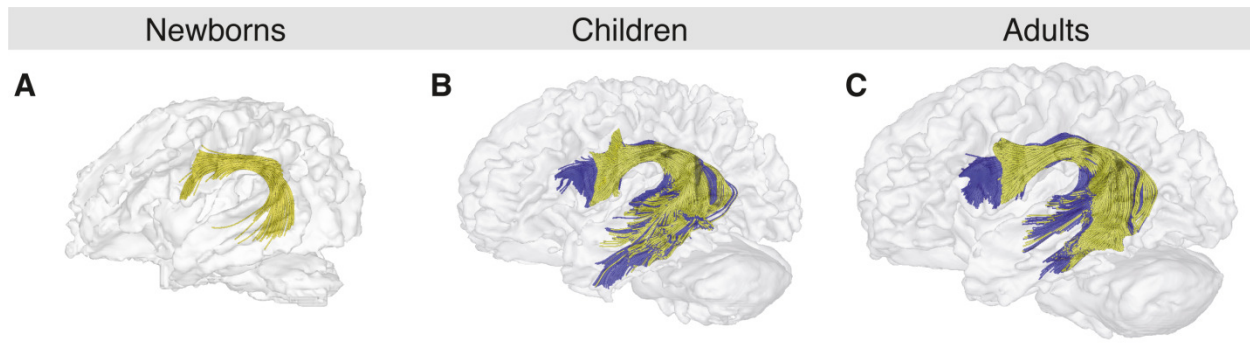


Fig. 1: The dorsal pathways of the language network in newborn infants, 7-year-old children, and adults. For newborns (A), no connection between the IFG and temporal regions is observed. Rather they only show a connection terminating in the premotor cortex. In addition to this dorsal pathway D1 (in yellow), children (B) also show a connection to the dorsal portion of BA 44 in the IFG, thus that dorsal pathway D2 (in blue) is present from at least childhood on. This connectivity pattern for children already closely resembles the one in the mature brain of adults (C) which show both dorsal pathways. The dorsal pathway D2 is assumed to play a crucial role in the processing of more complex linguistic functions, an ability that develops at about 7 years of age. Figures (A) and (C) after Perani et al. (2011).

For the ventral pathway, we aimed to separate the superficial tract (V1) and the deep tract (V2). The superficial tract (V1) as characterized by its connection to BA 45 in the IFG, was clearly apparent and easy to identify in adults and in children. The parieto-occipital ending of this component appeared more concentrated in the group of children compared to adults which might be related to an overall reduced number of streamlines in this component. This tract was also observed in infants and clearly distinguished from other components of the IFOF but it was weaker than in children and adults (Fig. 2, A-C, in green). Comparison of the number of streamlines for V1 showed 2592 streamlines for adults, 330 for children and 58 for infants. The deep tract (V2) was also identified in all three groups. In adults and children it was clearly advancing into the further frontal regions connecting to the SFG, MFG, DLPFC, and OFC. For infants, its middle and anterior connections were much shorter and did not reach as far as was observed in children and adults.

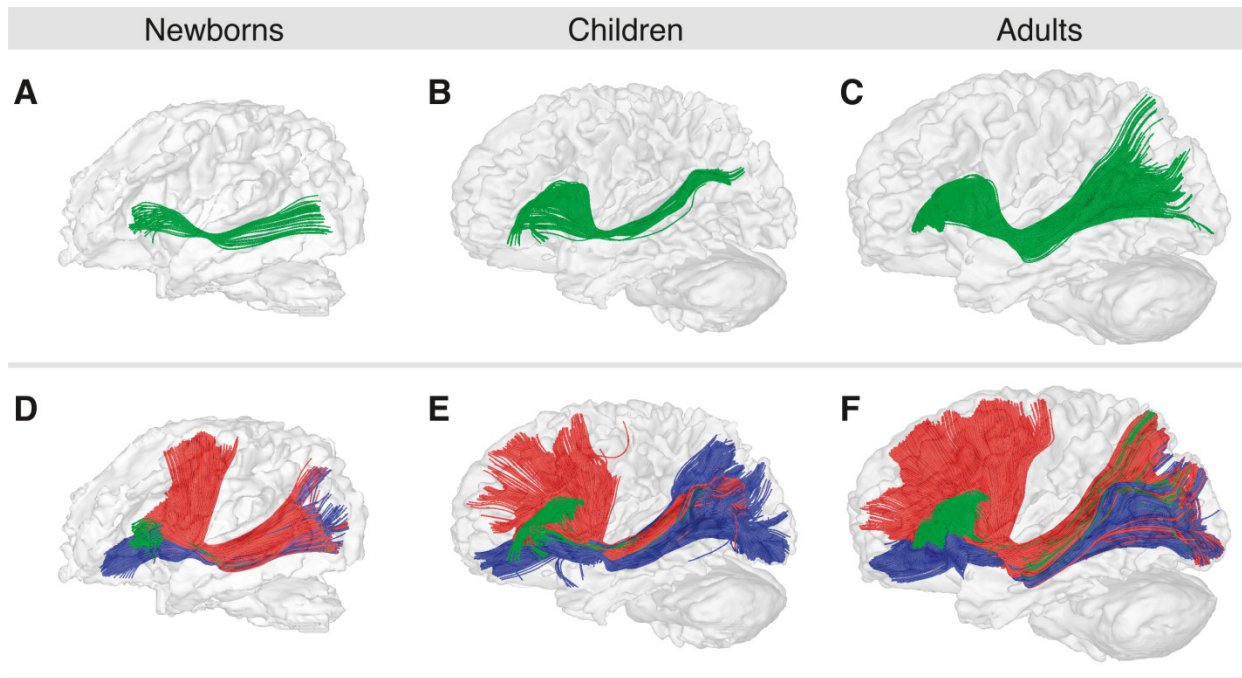


Fig 2: The ventral pathway of the language network in newborn infants, 7-year-old children, and adults. In newborns (A), the superficial tract (V1) of ventral pathway directed to BA 45 in the IFG (IFOF_{lat}, in green) is already in place, though much weaker than in children (B) who show only small differences in this connectivity pattern compared to adults (C). Thus, the superficial tract (V1) is the only fronto-temporal connection from the temporal cortex to the IFG in the language network of infants. For all three groups, the deep tract (V2) of the ventral pathway can be separated into at least two subcomponents (D-F): an anterior component connecting to the orbito-frontal cortex and frontal pole (IFOF_{orb}, in blue) and a posterior component (IFOF_{dors}, in red). For the deep tract (V2) there are no differences between the three groups.

We also aimed to differentiate the three subcomponents of the deep tract (V2), as described in Sarubbo et al. (2011). In all three groups, the anterior component directing to orbito-frontal cortex and frontal pole was clearly separated (IFOF_{orb} in blue, Fig. 2 D-F) from the middle and dorsal components. However, we were unable to unambiguously differentiate between the latter two components in any of the three groups. Thus, we treated them as one subcomponent directed to SFG, MFG, DLPFC and PMC (IFOF_{dors} in red, Fig. 2 D-F). The resulting two observable components of the deep tract V2 were clearly differentiated in all three groups. Although we were not able to unambiguously differentiate between the middle and the posterior

subcomponents of V2, it was evident that in infants the tracked connection to the MFG was shorter than the connection to the posterior SFG and PMC.

Statistical comparison was conducted in order to test for significant differences in mean FA between the three groups and the four tracts observable in all groups. Corresponding means are displayed in Fig. 3. ANOVA revealed significant main effects for the factor tract: $F(3,108) = 15.9, p < .001$, and group $F(2,36) = 47.5, p < .001$ and a significant interaction $F(6,108) = 7.0, p < .001$. Children showed significantly higher FA values across all tracts (FA = .43, SD = .019) than infants (FA = .26, SD = .018) and significantly lower values than adults (FA = .48, SD = .020). The lowest FA was observed in the dorsal pathway D1 of infants (FA = .23, SD = .015) and highest FA was observed in the dorsal and orbital portions of adults' IFOF (FA = .49, SD = .020). Dorsal pathway D2 was, unlike in infants, evident in children and adults. Statistical comparison between the two latter groups reveal that although this tract is in place in children (FA = .42, SD = .024) similarly to adults (FA = .48, SD = .020), it is still not fully mature in children: $t(1,18) = 5.8, p < .001$.

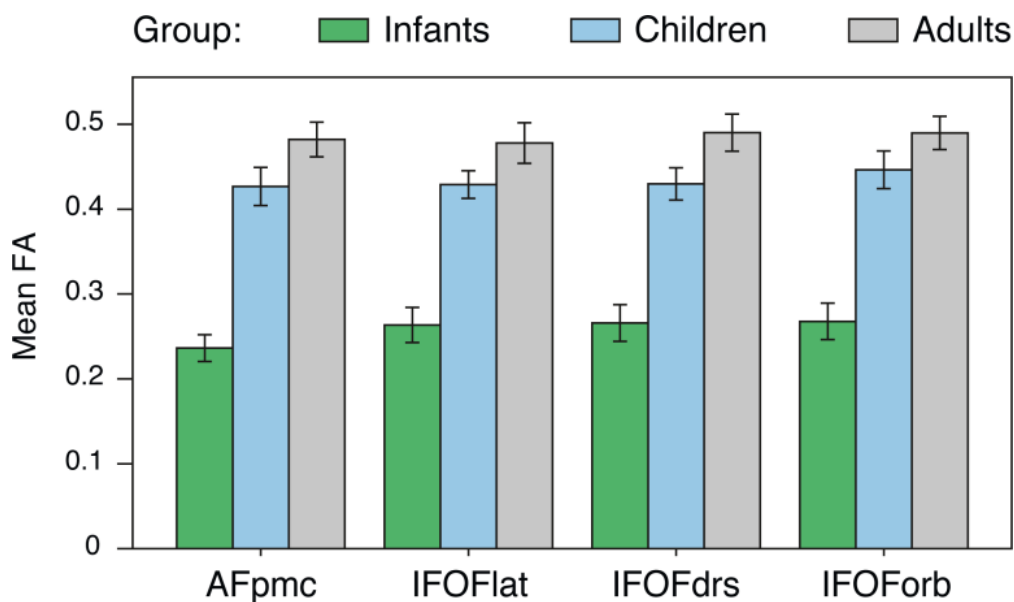


Fig. 3: Mean FA values for the dorsal pathway D1 (AFpmc) and the three components of the ventral pathway (the lateral portion of the IFOF: IFOFlat (V1), the dorsal portion of the IFOF: IFOFdrs (V2), and the

orbital portion of the IFOF: IFOForb (V2) in infants, children, and adults.
Infants show lowest FA values for all tracts, while adults show highest.

In order to test whether the observed smaller anisotropy for fiber tracts in newborns is specific for fronto-temporal fiber pathways or whether this is a reflection of the general immaturity of the infant brain white matter, FA in fronto-temporal white matter (averaged across all four tracts present in all age groups) was compared to the mean FA across the whole cerebral white matter skeleton. In a 2 (white matter, WM) \times 3 (Groups) ANOVA, newborns' FA in fronto-temporal pathways (FA = .255, SD = .018) was slightly but not significantly smaller than white matter mean FA (FA = .260, SD = .012). For children and for adults, fronto-temporal FA (children: FA = .429, SD = .019; adults: FA = .484, SD = .020) was significantly higher than mean FA (children: FA = .347, SD = .019; adults: FA = .390, SD = .014). This was reflected in a Group \times WM interaction ($F(2,35) = 43.7, p < .001$).

Fiber tracking and group comparison can be affected by individual variability, measurement noise, or crossing fibers. However, group-level tracking results were confirmed on the individual level for the present comparison. Sample data for the dorsal connection from three randomly selected individuals from each group are presented as Suppl. Content. Individual data confirmed that tract D2 was not present in any of the newborns, while it was clearly distinguishable in all children and adults. Moreover, we added 3D views for the group tracking results which can be rotated and allow a closer and detailed inspection of the data (see Suppl. Content).

4 Discussion

There are two main fiber connections in the language network connecting temporal and inferior frontal language-relevant areas in the brain, a dorsal one via the AF/SLF and a ventral one via the IFOF/ECFS. In the present study, we analyzed the maturation patterns of these pathways across three age groups, infants at birth, 7-year-old children, and adults.

Both streams consist of pathways and tracts with different structural terminations and functional roles. Dorsal pathway D1 terminates in the PMC and has been proposed to be relevant for auditory-motor integration which is important for early language

learning (Friederici, 2011). Dorsal pathway D2 terminates in the dorsal IFG in BA 44 of Broca's area and was proposed to be relevant for more complex linguistic functions (Brauer et al., 2011).

The two dorsal pathways show a distinct pattern of maturation during ontogeny. Dorsal pathway D1 is evident from very early on in life and it was observable in newborn infants, unlike dorsal pathway D2 which was not observable in this age group (Perani et al., 2011). In our analysis, however, we showed that pathway D2 is present in children at age 7. The tracking result for children was clearly different from that of newborn infants and rather resembled that of adults.

Nevertheless, it is important to note that although the termination of the dorsal pathway D2 in the dorsal IFG appears complete in children, it is still not yet fully mature as reflected in significantly lower FA for this tract at age 7 compared to adults. It is at around this age that children start to successfully process more complex and also passive sentence structures (Hahne et al., 2004) or object-first constructions (Dittmar et al., 2008; Knoll et al., 2012), functions suggested to be supported by the dorsal connection to BA 44 (Friederici, 2011).

The ventral pathway contains two tracts, a superficial tract (V1) terminating in BA 44 in the IFG and a deep tract (V2) terminating in the prefrontal cortex in the DLPFC, PMC, MFG and OFC. Unlike for the dorsal pathways, for the ventral pathway the tract connecting the language-relevant cortices, i.e., tract V1 terminating in BA 45, reveals a fast maturation and is already evident in newborns but still immature as indexed by FA. Also deep tract V2 can be identified in newborn and already shows the same connections as evident in adults. However, the tracking shows that it is the most posterior part of the frontal terminations, connecting to the PMC, SFG and DLPFC that show the longest terminations, while the terminations to the MFG and OFC are shorter. For children and for adults these terminations reach farther into the more anterior part of the frontal lobe in fiber tracking.

The middle and the posterior component of the IFOF's deep tract V2 were not unambiguously separable in our analysis. Therefore, we treated them as one component.

Nevertheless, based on their terminations, they can be roughly differentiated. Note that the posterior component terminating in the PMC, DLPFC, MFG and SFG as

shown in our data is not always included as part of the IFOF in some studies (Vandermosten et al., 2012 and Voineskos et al., 2010) while it is included in others (Lebel & Beaulieu, 2011; Lebel et al., 2012; Sarubbo et al., 2011 and Thiebaut de Schotten et al., 2012). This discrepancy is probable a result of different tracking protocols and procedures (for a discussion on tracking protocols, see Gierhan, 2013). The inclusion of these most posterior frontal connections is in accordance with *ex vivo* dissection data (Martino et al., 2010 and Sarubbo et al., 2011).

Besides the undetectable dorsal D2 connection, our newborn data revealed that also the white matter in the ventral fronto-temporal connections is delayed in its maturation. While adults and also children (though not yet on adult level) show higher FA in these pathways than in mean FA across the cerebral white matter, this is not the case for newborns. This result is consistent with previous findings on white matter maturation that showed slower myelination in language-related fronto-temporal regions compared to sensory or motor related white matter (Pujol et al., 2006).

For both, the dorsal and the ventral stream, the core language-relevant tracts terminating in Broca's area in the IFG can be considered as subcomponents of the two streams, i.e. as specific pathways or tracts within the streams (Rauschecker & Scott, 2009). It is the ventral pathway connecting the ventral part of the IFG and BA 45 to the temporo-parietal region of the language network that is in place very early. This result argues for an initial prominence of the ventral pathway (together with the dorsal pathway D1 connecting to the premotor cortex) in the language processing network during ontogeny. The dorsal pathway D2 connecting to Broca's area unfolds its involvement in higher language functions only during further development and is evident in 7-year-old children but not in newborn infants. On the basis of the present data, we cannot specify from what exact age this pathway connecting to BA 44 is in place. We argue that dorsal pathway D2 is necessary for more complex linguistic processes and would therefore be observable in early childhood, but not in infancy. It is important to note, however, that not delineating a fiber tract in DWI data by tractography does not imply this tract is missing in the brain. But compared to all other fiber pathways investigated in the present study that could be tracked in newborns, this tracking was not possible for dorsal pathway D2. This suggests that D2 in newborns conveys properties that differ from other age groups and also from

other pathways in newborns. We argue that the underlying reason is the pathway's immaturity as reflected in low FA.

Information exchange between frontal and temporal language regions can be guaranteed via the ventral pathway in cases where the dorsal pathway is not fully available, either due to brain lesions (Wilson et al., 2011), or due to structural immaturity in development (Brauer et al., 2011). The relevance of the ventral pathway for language processing has further been evidenced by a study with healthy adults that revealed that individual FA differences in the extreme and external capsule region of the ventral pathway correspond to individual abilities in word segmentation and grammar rule-learning under articulatory suppression which was used to tax the dorsal phonological memory system (Lopez-Barroso et al., 2011). Additional evidence for an involvement of the ventral pathway in language learning comes from a study in 8-10 year old children which reported higher FA in the ventral pathway along the IFOF in bilingual compared to monolingual children (Mohades et al., 2012).

The strong reliance on the ventral pathway during language development might also yield particular processing strategies. The involvement of the ventral inferior frontal areas in semantic processes was described in functional imaging studies for adults (Vigneau et al., 2006) and also for children (Sakai, 2005). The connection from the ventral IFG to the temporal cortex via the IFOF that was proposed to serve as a route for semantic processes (Duffau et al., 2005). The observed dominance of semantic strategies in sentence comprehension during early language development (Bates et al., 1984) is in line with the idea that the ventral pathway is a primary connection within the language network during early development. However, these functional consequences of white matter maturation were not directly testable within the present pure anatomical study.

Bringing together results from studies on a ventral connection between the temporal lobe and the IFG requires some consideration of findings concerning the ECFS and IFOF. The IFOF runs via the EmC/EC and is widely accepted to include terminations in the ventral IFG (Catani et al., 2002; Forkel et al.; Thiebaut de Schotten et al., 2012 and Vandermosten et al., 2012). This connectivity is identical to the connectivity of the superficial tract V1, as defined by *ex vivo* dissection (Martino et al., 2010 and Sarubbo et al., 2011). The ECFS is suggested to run via the EmC connecting the

IFG to the temporal lobe. In DTI data it is difficult to clearly separate the EC and EmC because of their size and proximity. Even in *ex vivo* dissection there is not always a clear cut between the two capsules and the fibers of the IFOF tracts probably run in both the EmC and EC (Sarubbo et al., 2011).

The present report comparing data from two studies has some limitations that deserve further discussion. The newborns' data were obtained at a different scanner than the children and adults' data. In order to ensure the reliability of the observed group differences in FA, we compared the infant data with data from a control group of adolescents and young adults obtained at the same scanner and using a very similar protocol adapted for adults. This comparison confirmed the findings from the original analysis (for details, see Suppl. Content). In the present comparison, group-level tracking was confirmed on the individual level. For instance, dorsal pathway D2 was absent in all of the newborn brains: conversely, it was present in the tracking results of every one of the child and adult brains (see Suppl. Content).

5 Conclusions

Our results support the view of a change in the fronto-temporal network from infancy to childhood with a later maturation of the dorsal compared to the ventral connection. Given the important role of the two connecting streams in the language network as shown in previous studies, we postulate an association between the time course of language development and the maturation of the fronto-temporal pathways, particularly the late maturation of the dorsal one. Tract V1 of the ventral pathway is the first one in the developing brain that connects the temporal and ventral inferior frontal language-relevant regions and is observable in newborn infants. For the dorsal pathways, pathway D1 terminating in PMC is already in place at birth. This pathway is likely to support auditory-to-motor mapping, which is necessary for auditory-motor feedback during babbling and language learning in infancy. Dorsal pathway D2 matures later and is evident in children, but, due to scarce myelination, not yet observable in newborns. This tract of the dorsal connection terminates in the dorsal IFG and is assumed to play a role in the development of more complex language functions.

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Supplementary content

Dorsal and ventral pathways in language development

Jens Brauer, Alfred Anwander, Daniela Perani & Angela D. Friederici

Supplementary methods

The newborns' data of the present study were obtained on a different scanner than the children's and adults' data. In order to ensure the reliability of the observed group differences in FA, we compared the newborns' data with data from a second control group of adolescents and young adults (N = 15, age = 18.5, range = 15 to 22) obtained on the same scanner with a very similar protocol adapted for adults (FOV 231 x 136 x 240, resolution 112 x 88, 59 slices, TE 58ms, TR 9.8s, 35 gradient directions). Tracking results were obtained for this control group according to the methods described in the main text. As for the original adult sample, all fiber pathways of interest were tracked. Compared to our original sample of adults (mean FA = 0.462), this younger sample showed slightly smaller FA values (mean FA = 0.437) (see Suppl. Fig. 1). Statistical comparison was conducted for the control vs. infant data obtained at the same scanner. A two (groups: infants, controls) by four (tracts: dorsal pathway D1: AF pmc, ventral pathways: IFOF lat, IFOF dors, IFOF orb) repeated measures ANOVA confirmed our original findings with significant main effects for group ($F(1,32) = 116.4, p < .001$) and tract ($F(3,96) = 51.5, p < .001$) and a significant interaction $F(3,96) = 36.9, p < .001$). This is consistent with the results of the original analysis.

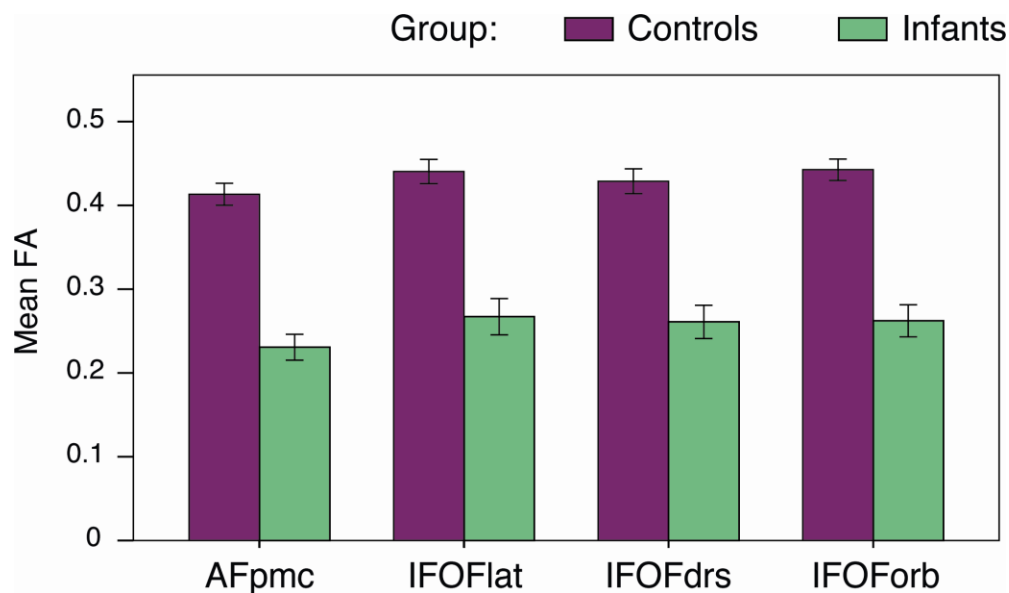
Furthermore, we compared signal-to-noise ratio (SNR) between newborns', children's and adults' data. SNR was extracted for white matter for the averaged B1000 image as described in Blank, Anwander, & von Kriegstein (2011). SNR was measured as the mean signal in the white matter divided by the standard deviation in a background region (free from ghosting or blurring artifacts). Values for three typical datasets were: adult: $SNR_{\text{mean b1000}} = 49.5$, child: $SNR_{\text{mean b1000}} = 52.6$, and newborn: $SNR_{\text{mean b1000}} = 34.9$. SNR was computed in the mean b1000 to take into account the variable signal intensities in the different diffusion gradients. In the mean image, the SNR increases approximately by the square root of the number of averages. Considering 60 directions in the adult and the child datasets and 21 directions in the newborn datasets, the estimated SNR values for a single b1000 image are rather comparable (adults: $SNR_{\text{single b1000}} = 6.4$, child: $SNR_{\text{single b1000}} = 6.8$, newborn: $SNR_{\text{single b1000}} = 7.6$).

The exact minimum of SNR for robust fiber tractography is difficult to determine. Jones and Basser (2004) proposed a minimum of 3 to avoid problems associated with the rectified noise floor in the estimation of the diffusion model. This corresponds to a SNR in the b0 image of $3/0.37 = 8.1$ (Jones, Knösche, & Turner, 2012). Smith and colleagues (2007) proposed a minimum SNR in the b0 image of 15 for tract-skeleton based analysis of derived measures like FA. Tractography has higher requirements on data quality than voxel based analysis to prevent the propagation of local errors and Fillard and colleagues (2011) recommend to use images with high SNR in order to obtain reliable tracking results. In this study,

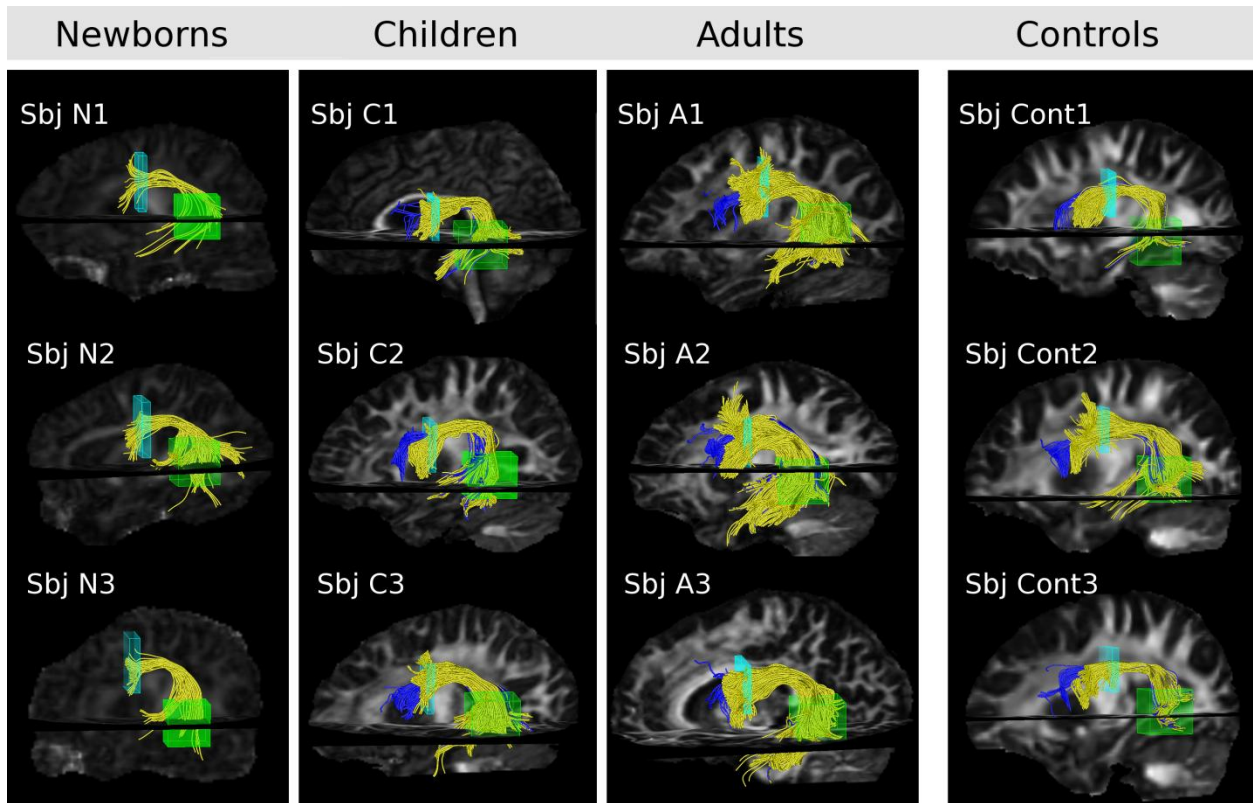
different tractography algorithms were evaluated with SNR in the b0 image of 15.8 (low) and 22.6 (high) and an SNR in the mean b 1500 image of 2.6 (low) and 17.6 (high). All mentioned recommendations are by far exceeded by every dataset in our samples. There is sufficiently high SNR in the present data for each group in order to obtain reliable high quality fiber tracking and evaluation of diffusion parameters. Also our single subject trackings (see Suppl. Fig. 2) support the quality of the results.

Another limitation of the study is a potential effect of the different voxel sizes used for newborns (1.4 x 1.4 x 2.0 mm) compared to children and adults (1.7 x 1.7 x 1.7mm). FA had been reported to be affected by voxel size (Oouchi et al., 2007). This study reported smaller FA in the SLF by 0.02 when increasing the voxel size by a factor of 3. However, this was reported for rather large differences in voxel size (2 mm vs. 6 mm), while the difference in the voxel size in the present analysis is much smaller. The large FA difference of 0.2 in the AF between newborns and adults cannot be explained by the variable voxel size.

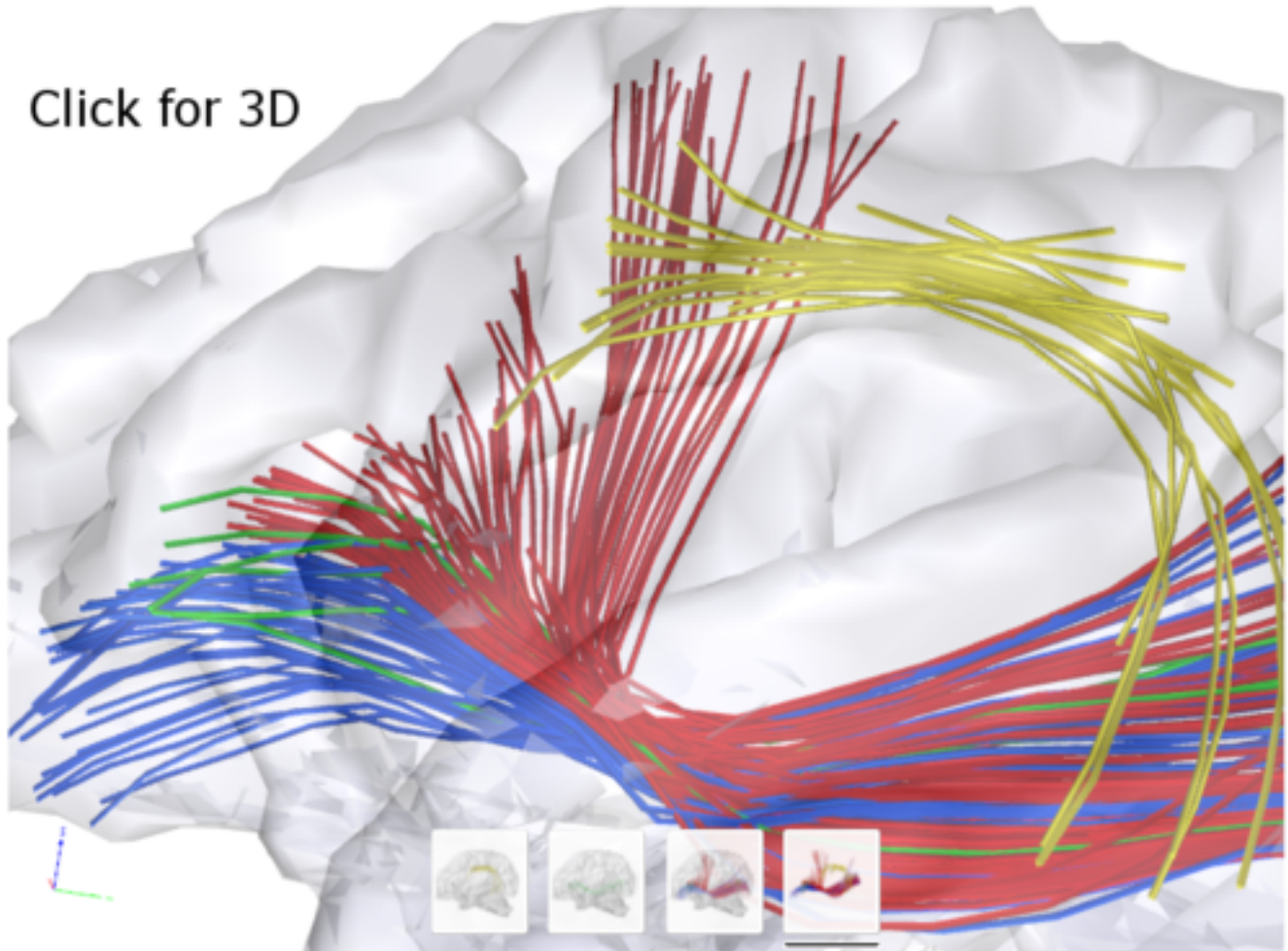
Supplementary figures



Supplementary Figure 1: Mean FA values for the dorsal pathway D1 (AFpmc) and the three components of the ventral pathway (the lateral portion of the IFOF: IFOFlat, the dorsal portion of the IFOF: IFOFdrs, and the orbital portion of the IFOF: IFOForb) for infants and the older control group obtained at the same scanner. Infants show lower FA values for all tracts, particularly for the AFpmc. This comparison confirms the results from the main analysis (see results).

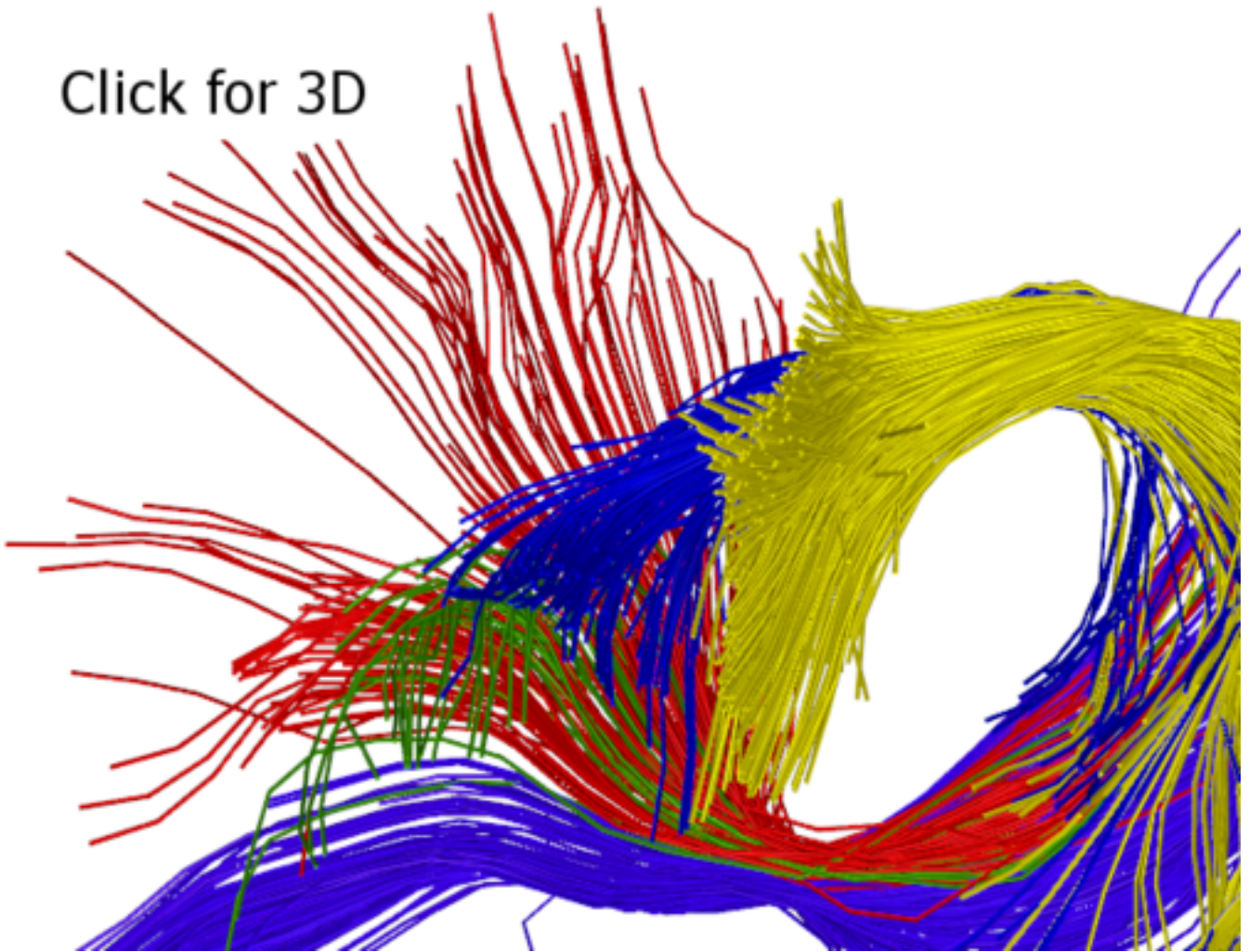


Supplementary Figure 2: Randomly selected samples of single-subject tracking results for the dorsal connection for three individual datasets from of the three groups (newborn infants, children, adults) as well as from the older control group obtained at the same scanner as the newborn’s data. In none of the newborns the D2 bundle (blue) connecting to the inferior frontal gyrus is traceable, while the D1 connection (yellow) to the premotor cortex can be tracked. Conversely, for all children and adults as well as the controls, both dorsal connections can be tracked. ROI-boxes for fiber selection in the frontal and temporal lobe are shown. They were positioned to segment the long segment of the arcuate fascicle according to Catani and colleagues (2005).



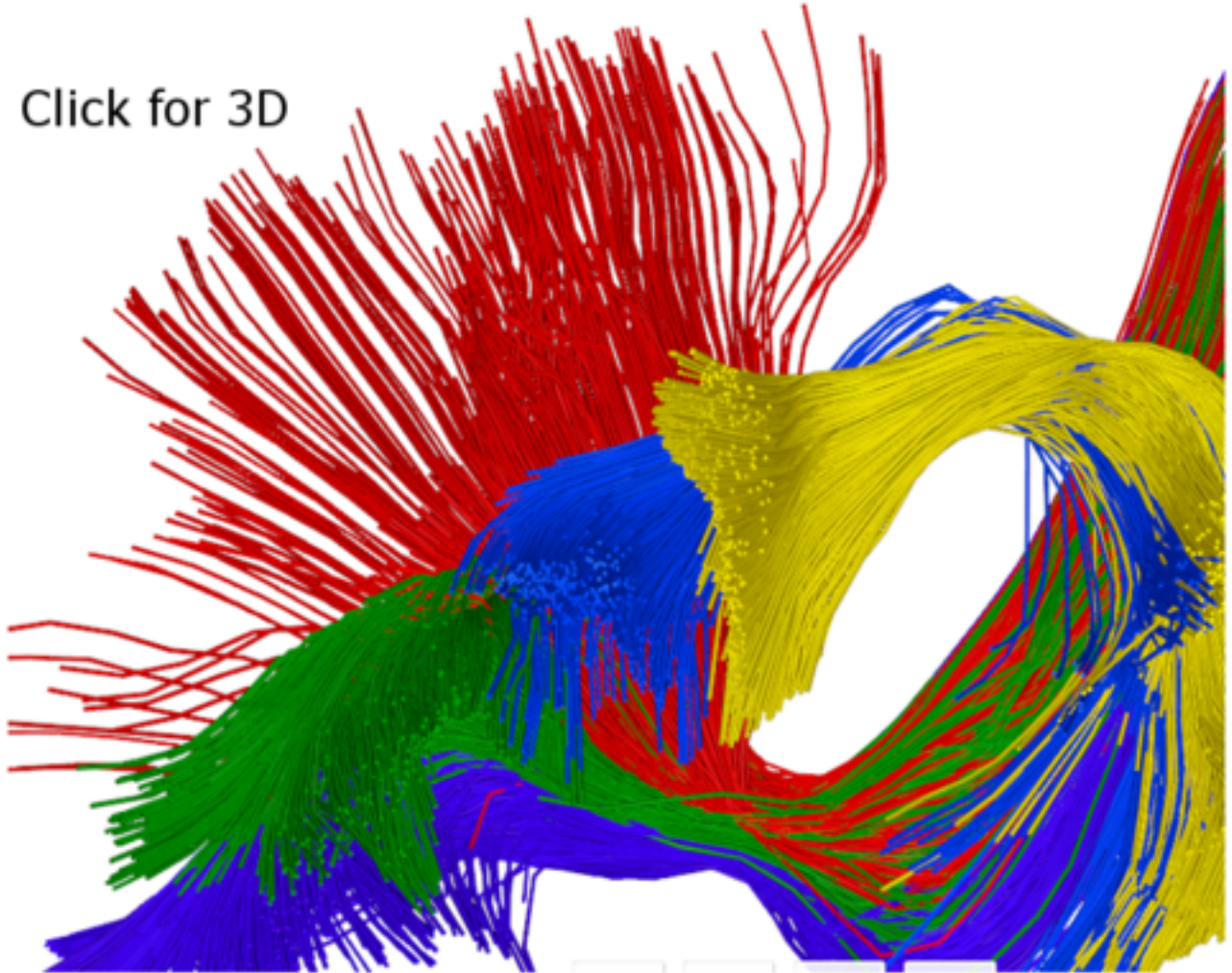
Supplementary Figure 3: A freely rotatable 3D view of tracking results for newborns for the dorsal pathway D1 (yellow), and for the ventral pathways V1 (green) and V2 (orbital branch: blue, dorsal branch: red). Every 1 out of 10 streamlines for each tract is represented. The 3D model in this figure was integrated in the portable document format (PDF) using SimLab Composer 2013 (SimLab Soft., Amman, Jordan) and requires the use of a compatible PDF reader (eg. Adobe Reader 9).

Click for 3D



Supplementary Figure 4: A freely rotatable 3D view of tracking results for children for the dorsal pathways D1 (yellow) and D2 (blue), and for the ventral pathways V1 (green) and V2 (orbital branch: blue, dorsal branch: red). Every 1 out of 10 streamlines for each tract is represented. The 3D model in this figure was integrated in the portable document format (PDF) using SimLab Composer 2013 (SimLab Soft., Amman, Jordan) and requires the use of a compatible PDF reader (eg. Adobe Reader 9).

Click for 3D



Supplementary Figure 5: A freely rotatable 3D view of tracking results for adults for the dorsal pathways D1 (yellow) and D2 (blue), and for the ventral pathways V1 (green) and V2 (orbital branch: blue, dorsal branch: red). Every 1 out of 10 streamlines for each tract is represented. The 3D model in this figure was integrated in the portable document format (PDF) using SimLab Composer 2013 (SimLab Soft., Amman, Jordan) and requires the use of a compatible PDF reader (eg. Adobe Reader 9).

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