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Language learning and brain reorganization in a 3.5-year-old child with left perinatal stroke revealed using structural and functional connectivity

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Abstract

Brain imaging methods have contributed to shed light on the possible mechanisms of recovery and cortical reorganization after early brain insult. The idea that a functional left hemisphere is crucial for achieving a normalized pattern of language development after left perinatal stroke is still under debate. We report the case of a 3.5-year-old boy born at term with a perinatal ischemic stroke of the left middle cerebral artery, affecting mainly the supramarginal gyrus, superior parietal and insular cortex extending to the precentral and postcentral gyri. Neurocognitive development was assessed at 25 and 42 months of age. Language outcomes were more extensively evaluated at the latter age with measures on receptive vocabulary, phonological whole-word production and linguistic complexity in spontaneous speech. Word learning abilities were assessed using a fast-mapping task to assess immediate and delayed recall of newly mapped words. Functional and structural imaging data as well as a measure of intrinsic connectivity were also acquired. While cognitive, motor and language levels from the Bayley Scales fell within the average range at 25 months, language scores were below at 42 months. Receptive vocabulary fell within normal limits but whole word production was delayed and the child had limited spontaneous speech. Critically, the child showed clear difficulties in both the immediate and delayed recall of the novel words, significantly differing from an age-matched control group. Neuroimaging data revealed spared classical cortical language areas but an affected left dorsal white-matter pathway together with right lateralized functional activations. In the framework of the model for Social Communication and Language Development, these data confirm the important role of the left arcuate fasciculus in understanding and producing morpho-syntactic elements in sentences beyond two word combinations and, most importantly, in learning novel word-referent associations, a building block of language acquisition.

1. Introduction

In the last decade, brain-imaging techniques such as functional magnetic resonance imaging (fMRI) and Diffusion Weighted MRI (DW-MRI) have largely improved our knowledge on the functional and structural brain changes observed in the healthy developing brain (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Dehaene-Lambertz & Spelke, 2015; Dosenbach et al., 2010; Perani et al., 2010, 2011; Shultz, Vouloumanos, Bennett, & Pelphrey, 2014). fMRI has been used to show that healthy newborns and young infants already exhibit robust bilateral functional activation in perisylvian networks, including superior temporal, inferior frontal and inferior parietal regions (Dehaene-Lambertz et al., 2002, 2006, 2010; Dosenbach et al., 2010; Mahmoudzadeh et al., 2013; Perani et al., 2011).

Interestingly, a recent model for social communication and language evolution and development (SCALED) has been proposed with the aim of integrating neuroanatomical and neurolinguistic data in a developmental and evolutionary framework (Catani & Bambini, 2014). In this model, specific hierarchically organized fronto-parietal-temporal networks in the left hemisphere underlie communicative and language related functions that sequentially develop with increasing linguistic complexity during the first years of life. Among the most important networks previously highlighted in other models of language processing (Bucich et al., 2004; Parker et al., 2005; Catani, Jones, & Fytche, 2005; Friederici, 2011; Hickok & Poeppel, 2007), the long segment of the arcuate fasciculus (AF), connecting frontal and temporal regions (including the classical Broca and Wernicke's regions) seems to be crucial for the proper development of linguistic skills (Lebel & Beaulieu, 2009; Budisavljevic et al., 2015). Importantly, this pathway is involved in word learning (Lopez-Barroso et al., 2013) and syntactic processing (Brauer, Anwander, Perani, & Friederici, 2013; Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006; Wilson et al., 2011). At the structural level, post-mortem and MRI studies have shown that white-matter fiber growth is already complete before the end of pregnancy, but that fiber pruning exist until the end of the first post-natal year (Dubois et al., 2015; Kostovic et al., 2014; Takahashi, Folkerth, Galaburda, & Grant, 2012). Indeed, while previous studies have pointed towards a delayed growth of this pathway in healthy newborns (Brauer et al., 2013; Perani et al., 2011; Zhang et al., 2007), a recent study suggests that this result might be related to a technical artefact of diffusion tensor imaging and tractography, due to the presence of crossing fibres from the the corticospinal tract and of the corona radiata, which might hamper the proper observation of the AF (Dubois et al., 2015). Moreover, although there is agreement in the literature regarding the delayed functional maturation of the dorsal stream for language processing (Brauer et al., 2013; Zhang et al., 2007, Dubois et al., 2015), especially when compared to the ventral one which connects the superior temporal, angular gyrus and inferior frontal gyri and is formed by the inferior fronto-occipital (IFOF), inferior longitudinal (ILF) and uncinate fasciculi (UF) (Bajada, Lambon Ralph, & Cloutman, 2015) recent data have shown that this maturational gap might be closed very early, even during the first weeks of post-term life (Dubois et al., 2015).

The fast post-natal changes observed in the long segment of the AF as well as of the anterior segment of the AF (connecting frontal and inferior-parietal regions) might be crucial for the early processes involved in language acquisition. Language experience modifies infants' initial sensitivities to speech sounds so by the end of the first year of life sensitivity towards native sound distinctions is not only maintained but even sharpened (Kuhl et al., 2006), while ability to discriminate nonnative sound contrasts has significantly decreased (Werker & Tees, 1984; see also Werker, Yeung, & Yoshida,

2012, for a general review of these perceptual narrowing processes). At the same time, speech production abilities appear very early following a similar developmental trajectory: while early “canonical babbling” (around 7-8 months of age) is still language general, the so-called variegated non-reduplicative babbling, usually appearing by the end of the first year of life (10-12 months of age), not only shows language specific properties (de Boysson-Bardies & Vihman, 1991; De Boysson-Bardies, 1993) but also shows an increase in the quality and tuning of the speech sounds produced (Kuhl & Meltzoff, 1996). As stated in the SCALED model, these language acquisition processes might require the functional maturation of the dorsal pathways in order to convey information from brain areas related to perception and production, especially between posterior superior temporal, inferior parietal and premotor and inferior frontal regions. Indeed, auditory-motor integration processes are needed for word repetition, word learning and for the development of verbal short-term memory (especially the brain regions supporting the phonological loop; Catani & Bambini, 2014). Finally, another important circuit highlighted in the SCALED model corresponds to the ventral temporalfrontal networks known to be involved in lexical and semantic processes (Friederici et al., 2006, Friederici, Kotz, Scott, & Obleser, 2010; Mazoyer et al., 1993; Mesgarani, Cheung, Johnson, & Chang, 2014; Price, 2012; Wilson et al., 2011). Its functional maturation might be related to the vocabulary spurt starting at around 18 months with up to nine new words learnt every day (Goldfield & Reznick, 1990; Schafer & Plunkett, 1998).

Despite a rather large body of literature on typically developing children, little is known on the effect of early brain lesion on the stepwise acquisition of linguistic functions in young children. In this context, patients who have suffered from early left hemisphere injury during the prenatal or perinatal period are of great interest, as they present individual differences in their degree of cognitive and language recovery (Anderson, Spencer-Smith, & Wood, 2011; Fuentes, Deotto, Desrocher, deVeber, & Westmacott, 2014; Murias, Brooks, Kirton, & Iaria, 2014). In terms of cognitive measures, several studies have pointed towards a relationship between the severity of the cognitive and linguistic deficits, the age of stroke or the size and the site of the lesion (Avila et al., 2010; Lansing et al., 2004; Max, Bruce, Keatley, & Delis, 2010; Westmacott, Askalan, MacGregor, Anderson, & DeVeber, 2010). In a large cohort study involving 145 children, Westmacott et al. (2010) compared the level of performance on age-appropriate Wechsler intelligence scales for children (WISC-III and IV, WPPSI-R and WPPSI-III) in three groups of patients who had unilateral stroke (cortical, subcortical and combined) during the perinatal period, early childhood and later childhood. Independently of the lesion location, the perinatal group performed more poorly than the early childhood group on verbal ability (verbal IQ). Compared to the later childhood group, the perinatal group had lower scores on overall intellectual ability (Full Scale IQ), auditory attention and mental manipulation (Working Memory index) and verbal ability (Verbal IQ). However, these authors did not find a significant effect of lesion laterality but instead, they found clear differences between subcortical, cortical and combined lesions with the poorest performance in the group of children with combined lesions. These results suggest that the site of the lesion can modulate the relationship between linguistic outcomes and the age of stroke. In terms of linguistic measures, speech production abilities have been studied in various groups of children with unilateral perinatal stroke. Despite heterogeneous groups in terms of age range, type and site of lesions, there is converging evidence showing that, compared to typically developing controls, these children present deficits in phonological, syntactical and semantic aspects of language production (Avila et al., 2010). Compared to controls, they generally produce shorter sentences despite normal vocabulary (Demir, Levine, & Goldin-Meadow, 2010), have lower mean

length of utterance (MLU; Chapman, Max, Gamino, McGlothlin, & Cliff, 2003; Rowe, Levine, Fisher, & Goldin-Meadow, 2009) and make more morphological errors (Reilly, Wasserman, & Appelbaum, 2013). Interestingly, Chilosi, Cipriani, Bertuccelli, Pfanner, and Cioni (2001) have assessed longitudinally the cognitive and linguistic functions in 18 patients with left or right perinatal stroke. While cognitive functions did not differ between the two groups at both 2 and 4 years of age, vocabulary was more delayed at the latter age in the left lesion group compared to the right lesion group. Importantly, these results confirm that children who had stroke very early in development are probably the most vulnerable to the negative effect of stroke on their cognitive and language outcomes (Fuentes et al., 2014). The observation that children with perinatal stroke may “grow into” their deficits (i.e., despite “normal” abilities early after the damage, new deficits may emerge over time as in Anderson et al., 2011; Dennis, 1989) may be related to the early disruption of the myelination process, particularly in the frontal lobes, which may impair higher and more complex cognitive and linguistic skills (Max, 2004).

Brain-imaging methods and research in animal models have also contributed to shed light on the possible mechanisms of recovery and cortical reorganization after early brain insult (Jordan & Hillis, 2011; Kolb, Mychasiuk, Williams, & Gibb, 2011; Krakauer, Carmichael, Corbett, & Wittenberg, 2012; Staudt et al., 2002; Stiles, 2000). In terms of functional activations, recent fMRI data collected in children and young adults with perinatal left-hemisphere brain lesions have shown that the undamaged right-hemisphere is able to take over language productive functions, showing cortical reorganization (Lidzba & Kraegeloh-Mann, 2005; Staudt et al., 2002; Tillema et al., 2008). For instance, Tillema et al. (2008) acquired functional data of 10 children with left perinatal stroke (6-16 years old) during a verb generation task. Compared to the matched control group, the stroke patients showed a clear displacement of the left frontal language production regions to the right hemispheric homologue regions. In another study, the participants with left hemisphere stroke who were recruiting additional left-brain regions during a category fluency task performed better than the participants largely recruiting right-hemispheric brain regions (Raja-Beharelle et al., 2010). In terms of functional activations for comprehension processes, to our knowledge, only one study has shown either bilateral activation in the superior and middle temporal gyri or right sided inferior and middle frontal gyri during a story listening task in 3 patients (7, 9 and 12 years old) with left hemisphere stroke (Jacola et al., 2006). Additionally, a recent study has revealed that increased posterior superior temporal gyrus inter-hemispheric connectivity during an audio-visual story telling task predicted better receptive language performance in 14 patients of 7 years of age who had prenatal or perinatal brain insults, but worse performance in typically developing siblings (Dick, Raja Beharelle, Solodkin, & Small, 2013). These tentative results temper the prevailing “right-hemisphere-take-over” theory and favor the idea that a functional left-hemisphere is crucial to achieve a normalized pattern of language development after left-perinatal stroke (Raja-Beharelle et al., 2010). At the structural level, while several studies have used DW-MRI to reconstruct the AF in adult patients with stroke (see for a review Jang, 2013) or in young children with cortical malformations (Paldino, Hedges, Golriz, 2015; Paldino, Hedges, Gaab, Galaburda, & Grant, 2015), to our knowledge, no published data exist on the effect of left perinatal stroke on the integrity of the dorsal and ventral streams at such a young age.

In order to provide further support to the idea that a functional left-hemisphere is crucial to achieve a normalized pattern of language within the framework of the SCALED model, we report the case of a 3.5-year-old boy, born at term with a left perinatal ischemic stroke of the left middle cerebral artery (MCA), affecting mainly the supramarginal gyrus, superior parietal and insular cortex extending

to the precentral and postcentral gyri and also covering small portions of the middle posterior part of the left superior temporal gyrus (see Fig. 1). Considering the SCALED model and the delayed functional maturation of the anterior and long segments of the AF during the postnatal period, we expected that a perinatal stroke of the left MCA affecting these segments would be accompanied by possible deficits in word learning and other language functions associated to the dorsal stream, while linguistic functions related to ventral fiber bundles would be spared.

2. Rationale and chronology of the study

With the aim of thoroughly following the impact of left perinatal stroke on language development, language learning capacity and processing abilities in the same child, we gathered standardized neuropsychological data at 25 and 42 months of age. For the purpose of the study, at the latter age, the child was also evaluated with specific fine-grained developmental measures of receptive and productive aspects of language and with a novel-word learning task. This extended assessment was planned to cover the different language domains that could be affected and could show developmental delays, from receptive to expressive language and from phonology to lexical and morpho-syntactic levels. Crucially, the capacity for novel-word learning and recall was assessed, an ability which is not usually evaluated in standard neuropsychological and language testing. Measures from the patient were compared to data from control groups of children comparable in terms of native language, educational level, cultural background and age (see Table 1).

Furthermore, to determine the impact of left perinatal stroke on both functional and structural neuroimaging data, the child was scanned under propofol anesthesia at 42 months. We used two different methods with an age-appropriate atlas to quantify the lesion extent and location. At the functional level, we used both a passive language listening fMRI task and a resting state session in order to assess the convergence of the fMRI results and to seek for a fronto-temporal resting state network that might capture language-related intrinsic connectivity. Even though several studies have shown that it is possible to measure task-related fMRI activity under sedation, the use of medication can sometimes lead to the failure to detect any activation at all (Bernal, Grossman, Gonzalez, & Altman, 2012) and may impact the identification of resting state networks at least in macaque monkeys (Bartfeld et al., 2015). Thus, we took into account the medication pharmacokinetics used for anesthesia to ensure that the functional tasks were carried exclusively under a very low level of medication.

At the structural level, we performed virtual “in vivo” fiber track dissections of the dorsal and ventral language pathways using deterministic tractography. Bearing in mind that also the ventral white matter pathways (ILF, and UF) are widely considered as associated with language processing (Hickok & Poeppel, 2007 ; Rauschecker, 2012 ; Saur et al., 2008 ; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011; also Forkel et al., 2014, Schmahmann et al., 2007, for a debate on the involvement of the IFOF for language processing and its correct anatomy in humans), we also performed virtual in vivo dissections for these tracts. Deterministic tractography was selected based on previous studies which successfully used this neuroimaging technique to relate AF structural integrity to language disorders in different clinical populations, including stroke (Forkel et al., 2014; Kim & Jang, 2013; Tuomiranta et al., 2014; for a review see Jang, 2013), primary progressive aphasia (Galantucci et al., 2011) and even in patients suffering from brain tumors (Bizzi et al., 2012; Sierpowska et al., 2015). In addition, recent studies in young children with cortical malformations (age range: 3-18 years old) have recently shown that the failure to dissect a left AF was a marker of language dysfunction (Paldino, Hedges, Golriz, 2015; Paldino, Hedges, Gaab, et al., 2015). Nonetheless, tractography methods pose some limitations when it comes to lesioned brains (Kristo et al., 2013) as the determination of fiber orientation becomes increasingly difficult in peri-lesional regions for both chronic and acute stroke, where necrosis and the presence of edema, respectively, can alter white matter microstructure (Møller et al., 2007). Thus, we used a high-resolution T1-weighted (T1-w) anatomical image to perform a track-wise lesion analysis in order to gather additional information, independently from the diffusion data and the in vivo

dissections, on which white matter pathways could be affected by the lesion. Finally, in order to assess whether the lesion also affected classical cortical language areas (in addition to language white matter pathways), we compared the lesion location with an fMRI meta-analysis of language-related activations.

3. Material and methods

a. Case description

The patient, a 3.5-year-old boy, was born from vaginal delivery at 38 weeks of gestation with a birth weight of 2770 g. The pregnancy was uneventful and no family history of arterial ischemic stroke was reported. He presented with right limbs clonic seizures at 42 h of life and during the next 3 days. The amplitude-integrated EEG showed a continuous background pattern and several electro-clinical seizures during the 90h he was monitored. He was treated with phenobarbital for 6 days. Brain MRI demonstrated a left arterial ischemic stroke involving the posterior branch (M4) of the Middle Cerebral Artery (MCA). The neurologic examination revealed no asymmetry in muscle tone, strength or in the myotatic reflexes. Heart and abdominal echo-Doppler performed at 62 h of age did not show any cardiac thrombus or vessel thrombosis in abdomen. The patient did not have clotting factor abnormalities and thrombophilia was excluded based on the following tests which were within the normal range: Protein C, Protein S, Factor V Leyden, anticardiolipin antibodies (ACAs), prothrombin G20210A, Antithrombin III, Lipoprotein a, homocysteine, MTHFR C677T mutation. There was no reported obstetric or neonatal complication considered to be risk factors of neonatal stroke, including birth asphyxia, preeclampsia, chorioamnionitis, cardiac anomalies, polycythemia, and systemic infection. As it usually occurs, the etiology of neonatal stroke in the present case remained unknown since definitive causes for most neonatal strokes have not been established. Although the patient has never showed any signs of hemiplegia, he was administered with physical therapy, one session every two weeks during the first 18 months of his life. Except this, the patient did not receive any other kind of rehabilitation or behavioral intervention. At the time of the study, the child showed a right hand preference and both parents were right-handed. The parents of the patient received information on the study in written and spoken form and their written consent was obtained. The study was approved by the Ethics Committee of the Hospital Sant Joan De Deu (CEIC PIC-85-13) and respects the Declaration of Helsinki.

b. Neuropsychological testing and word-learning task

Cognitive, motor and language development assessment was performed twice, at 25 and 42 months of age, using the Bayley Scales of Infant and Toddler Development, third edition (Bayley, 2006; BSID-III). The test provides separate scaled and composite scores for each developmental domain (Cognitive, Motor and Language). The language scale is composed of receptive and expressive communication subtests. Scaled scores are derived from the subtests total raw scores, ranging from 1 to 19, with a mean of 10 and a standard deviation of 3. Composite scores are scaled to a metric with a mean of 100 and a standard deviation of 15. Composite scores between 90 and 110 fall within the average range.

Receptive vocabulary was assessed at 42 months of age using the Peabody Picture Vocabulary Test, 3rd edition (Dunn, Dunn, & Arribas, 1997; PPVT-III, with Spanish norms), suitable for infants from 2 years of age. The test offers a raw score that can be transformed into a percentile rank, a verbal IQ (mean = 100 and SD = 15) and the corresponding developmental age.

i. Expressive language measures

Phonological development was assessed using a tool that offers normative segmental data for Spanish-speaking children aged 3-7 years (Bosch, 2004). The tool was designed to

assess phonological production of 32 common words, mostly disyllabic, involving 15 different word shapes and covering all consonantal segments and segment combinations in Spanish. Words are elicited from pictures favoring utterance production rather than simple naming. From the child's spontaneous production a developmental profile can be established (three levels: average, delayed and disordered phonology). Quantitative measures such as Phonological Mean Length of Utterance (pMLU) and Phonological Whole-Word Proximity (Proximity) scores can also be obtained, for complexity and closeness to the target productions, respectively, following Ingram (2002). The pMLU of the word list from this tool is 8.31. This would be the value obtained if all target words were correctly produced, the Proximity score in this case (child's pMLU/target pMLU) being 1. Analysis of the original data from the sample (N = 50) of 3-year-old children (age range from 3 years to 3 years 11 months) from Bosch (2004), to be used as a reference group, yielded the following values: mean pMLU 7.55 (SD = .55) and mean Proximity score .91 (SD = .064).

Expressive language complexity was assessed from the recording of the spontaneous speech produced in a free conversation/play situation using pictures and toys. The parents were present during this session, thus favoring a natural conversation setting. The child's spontaneous utterances were extracted from the recording and transcribed so that the values of the Mean Length of Utterance in words (MLU) and the MLU of the five longest utterances (max-L) could be obtained. These measures could then be compared to those from an age matched control group of N = 50 Spanish-speaking children at age 3.5 (Fernandez & Aguado, 2007). Data from this control group can be considered as reference values for the general population at 3.5 years of age for MLU and max-L, thus useful for the present comparison. Parents' educational level (as a proxy for SES) of the control sample was distributed into high (48%), medium (36%) and low (16%), thus representing different levels of education as found in the general population. Mean MLU in words for this reference group is 3.5 with a standard deviation of .57. Mean value of the max-L score is 9.07 (SD = 2). Additionally, the "sentence repetition" subtest from the NEPSI-II (Korkman, Kirk, & Kemp, 2007, Spanish adaptation) was also administered to assess the ability to produce utterances of increasing complexity after a model. For this subtest the scaled score had a mean of 10 and standard deviation of 3.

Word-learning ability was assessed with a task designed to measure fast mapping and recall of multiple novel word-object associations adapted from Experiment 2 in Horst and Samuelson (2008). It involved a) a referent selection phase with ostensive naming and labeling of the target elements after correct selection, and b) two recall phases, one immediately following the referent selection phase and the other after a 5-min's delay (i.e., immediate and delayed recall phases). The objects were presented twice, in two different contexts, each involving different foils, thus providing the necessary experimental control to more adequately assess children's multiple word learning capacity and increasing task validity for this specific test of word learning (see Axelsson & Horst, 2013). An ostensive procedure was used to maximize word learning via fast mapping and to favor that the proportion of correct selection responses in the recall phases could reliably be above chance level.

In the initial referent selection phase (fast mapping) four novel labels ([gomi], [flas], [binoko] and [kufeta]), all of them phonotactically acceptable word-forms in Spanish, were successively introduced. Eight trials were used, but only four of them involved a novel label in the context of two known objects and a non-familiar one. These fast-mapping trials alternated with trials presenting three familiar objects from the set used in this task [a flower, a cow, a horse, a car, a feeding bottle, a ball, a cap and a spoon]. Only four of the eight familiar objects were requested. The remaining unnamed familiar objects served as foils in the retention phase.

After correct object selection, the experimenter produced a fixed set of utterances naming the novel object twice and requesting the child to name it after him (e.g., “yes, this is a flas. The flas is small and it makes some noise. Can you name it?”). This mapping phase was followed by an immediate recall test with eight test trials in which the child was asked twice to select each of the four novel name-objects previously mapped (presented in the same order as in the mapping phase to keep the same temporal distance for all words), but this time the arrays involved two novel objects and a familiar one. Each correct selection of the newly learned words scored 1 (maximum score 8). A second measure reflecting total number of words learned (maximum score 4) was also computed: a score of 1 was only given if the child was correct in choosing the target object twice, in both test trials involving different sets of objects. Finally, after a delay of 5 min during which the child was engaged in a non-linguistic task (copying and coloring drawings of geometrical shapes) the delayed recall phase of the task was administered, repeating the same sequence of trials as in the immediate recall phase and using a similar scoring procedure.

Data from a typically developing school age-matched control group of children (N = 10, 5 boys) from the same age, same maternal language, educational level, cultural background and geographical area were obtained. Socio economic status was determined by the highest educational level attained by each parent and was assessed in all participants as well as in our patient. Levels ranging from 1 to 4 reflected no school, primary school, secondary school and university degree, respectively. Children in the control group were tested with exactly the same procedure as the patient (ostensive condition) and following the same order of presentation of trials in the mapping and recall phases.

Data from the patient were compared with the level of performance of the school age-matched control group, from the same age, same family language, geographical area and socio-economical status. The comparison was performed using the Crawford test which is specifically designed to compare a patient to a small sample of control participants (Crawford, Garthwaite, & Porter, 2010). No significant differences were found regarding age: control group ($m = 42.1$ months; $SD = 2.47$) versus patient (42 months) [Crawford test, one tailed, $t = .04$; $p = .48$]. No significant differences were found regarding the socio-economical status neither, based on the highest educational levels attained by the parents on a scale from 1 to 4 [Crawford test, one tailed, $t = .837$; $p = .354$].

c. MRI procedure

i. Sedation procedure

In order to reduce movement artefact of the patient during the MRI examination, the child was previously sedated as recommended in pediatric functional neuroimaging (Bernal et al., 2012; DiFrancesco, Robertson, Karunanayaka, & Holland, 2013 ; Kerrssens et al., 2005 ; Lai, Schneider, Schwarzenberg, & Hirsch, 2011 ; Souweidane et al., 1999). The patient was evaluated by the anesthesiologist and food intake restriction was controlled. First, and with the aim of acquiring structural MRI information (structural MRI and DW-MRI sequences require precise and careful control of infant head and body movements), anesthesia was induced via a mask with sevoflurane which is the routine method used in Sant Joan de Deu Hospital. Immediately after this procedure, the intravenous line was placed and the child was transitioned to an intravenous-based anesthetic with propofol. The initial propofol dose was adjusted to render the patient motionless but able to maintain his or her airway with a laryngeal mask. Propofol dosage for induction was 2 mg/kg and after perfusion, a dosage of

8-10 mg/kg/h was administered. Dosage was decreased to 6 mg/kg/h until the end of the procedure. Both, sevoflurane and propofol have very small side effects and are drugs routinely used in pediatric neuroimaging. Duration of sedation using both drugs is very small allowing for very fast recovery times (Bernal et al., 2012). Importantly, we took into account the pharmacokinetics of sevoflurane in order to ensure that functional tasks were carried exclusively under propofol anesthesia. Because of this, we induced a fast transition to propofol anesthesia after sevoflurane and also we ran the first 18 min of the structural imaging part ensuring that the possible effect of sevoflurane in subsequent fMRI task was minimum. Indeed, the low solubility in blood of sevoflurane induces a rapidly decreasing alveolar concentration after cessation of the inhaled agent which is linked to very fast recovery times and wash out (Bernal et al., 2012; Yasuda et al., 1991).

ii. MRI scanning

MRI data was collected on a 1.5 T whole-body MRI scanner at Hospital Sant Joan de Deu (Barcelona, GE Signa HD). The acquisition of a high-resolution T1-w structural image (magnetization-prepared rapid-acquisition gradient echo sequence; TR = 12,396 msec, TE = 5.22 msec, slice thickness = .4297 mm, 1 mm in plane resolution, 180 slices, matrix size = 512 512) was followed by a DW-MRI sequence. DW-MRI scans were acquired with a spin-echo echo-planar imaging (EPI) sequence (TR: 16,500 msec, TE: 100 msec, 48 axial slices, slice thickness 2.5 mm, FOV: 270, acquisition matrix: 100 100, reconstruction matrix: 256 256, voxel size: 1.05 1.05 2.5 mm³). One run with one non-diffusion weighted volume (using a spin-echo EPI sequence coverage of the whole head) and 29 diffusion-weighted volumes (b-value of 1500 sec/mm²) was acquired. One final FLAIR image (TR = 11,002 msec, TE = 9 msec, slice thickness = .3711 mm, 4.5 mm in plane resolution, 35 coronal slices, matrix size = 512 512) was also collected. After structural data was collected, an fMRI language task was carried out. One functional run consisting of 120 (6 min) functional images sensitive to blood oxygenation level-dependent contrast (BOLD; echo planar T2*-weighted gradient echo sequence; TR = 3000 msec, TE = 60 msec, flip angle 80, acquisition matrix = 64 64, 3.75 mm in-plane resolution, 3.5 mm thickness, no gap, 34 axial slices aligned to the plane intersecting the anterior and posterior commissures) was acquired. Additionally, 100 volumes (5 min) of resting state (no stimuli were presented during acquisition) were collected using the same acquisition parameters as for the language task.

d. Precise lesion localization

In order to accurately determine the lesion location, we performed two independent analyses. Since the normalization of pediatric MRI data to adult templates and atlases has several limitations (see for instance Altaye, Holland, Wilke, & Gaser, 2008), we used an age-appropriate template to register the patient's MRI images to an atlas (Richards, Sanchez, Phillips-Meek, & Xie, 2015). In particular, we employed FSL's FNIRT (FMRIB's Nonlinear Image Registration Tool; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), to normalize our patient's T1-w and its corresponding lesion mask to a 3-year-old MRI brain template obtained from the Neurodevelopmental MRI Database (<http://jerlab.psych.sc.edu/NeurodevelopmentalMRIDatabase/access.html>; Almli, Rivkin, & McKinsty, 2007; Fillmore, Richards, Phillips-Meek, Cryer, & Stevens, 2015; Richards et al., 2015; Sanchez, Richards, & Almli, 2011). We first linearly registered the patient's T1-w and the corresponding lesion map

to the 3-year-old template using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson et al., 2012). Then, we used FNIRT to non-linearly register the patient's images to the aforementioned age-specific brain template. For all these steps, cost function masking was employed (Andersen, Rapcsak, & Beeson, 2010; Brett, Leff, Rorden, & Ashburner, 2001; Ripolles et al., 2012). Finally, we used the 3-year-old adapted LONI LPBA40 brain atlas included in the Neurodevelopmental MRI Database (Richards et al., 2015; Shattuck et al., 2008), to identify the specific brain areas affected by the lesion. In addition, to provide a measure of gray and white matter loss, we computed an estimation of the lesion size (Tillema et al., 2008) as follows. We segmented the T1 images into GM and WM using the 3-year-old gray and white matter segmentation priors included in the Neurodevelopmental MRI Database (Richards et al., 2015) using Unified Segmentation (Ashburner & Friston, 2005). The cerebellum and brainstem were then masked out using the manual 3-year-old atlas of the Neurodevelopmental MRI Database (Fillmore et al., 2015; Richards et al., 2015). The ratios between the total GM and WM volume in both left and right hemispheres were computed and converted to a percentage of left cerebral hemisphere loss due to stroke (Tillema et al., 2008). Recent evidence shows that although there are differences between left and right GM/WM volumes in healthy controls, these should not exceed 1% (Carne, Vogrin, Litewka, & Cook, 2006).

e. Track-wise lesion analysis

Although in vivo virtual dissections have been shown to be a successful method to assess white matter integrity after stroke in adults (Jang, 2013), this technique presents several limitations due to the presence of the lesion (e.g., correct detection of fiber orientation in peri-lesional regions or in areas with presence of multiple crossing fibers; Kristo et al., 2013). Therefore and taking into account the limitations of the acquired diffusion data (29 directions), we also performed a track-wise lesion analysis based on a method that uses an atlas of human adult white matter tracks (Tractotron toolbox; Thiebaut de Schotten, Dell'Acqua, et al., 2011 ; Thiebaut de Schotten, Ffytche, et al., 2011 ; Thiebaut de Schotten et al., 2014). This method allowed us to gather additional information, independently from the DW-MRI data, on the integrity of the left AF. The Tractotron toolbox (Catani et al., 2012; Thiebaut de Schotten, Ffytche, et al., 2011 ; Thiebaut de Schotten, Dell'Acqua, Valabregue, Catani, 2012 ; Thiebaut de Schotten et al., 2014) uses lesion maps in MNI space to provide a percentage of likelihood for a specific tract to be disconnected, thus providing more information to describe the pattern of damage induced by the lesion. First, a lesion mask was drawn by P.R. (who already had experience in stroke lesion identification; Ripolles et al., 2012), using the FLAIR image in native space, and the MRlcron software package (Rorden & Brett, 2000; <http://www.cabiatl.com/mricro/mricron/index.html>). Then, the FLAIR image and the lesion mask were coregistered and resliced to match the T1-w. The lesion mask was finally registered to the adult MNI152. However, the use of adult templates for pediatric data normalization has several limitations (Altaye et al., 2008; Richards et al., 2015; Sanchez et al., 2011). In addition, accuracy between registration methods varies greatly (Klein et al., 2009), specifically for lesioned brains (Ripolles et al., 2012). Taking into account these considerations, we used two different normalization approaches to register our lesion map to the MNI space. Firstly, we used SPM Unified Segmentation (Ashburner & Friston, 2005), a registration algorithm which is based on an iterative process that combines image registration, tissue classification and bias correction to produce nonlinear registration to a set of tissue probability maps (using around 1000 cosine basis functions; Ashburner & Friston, 2005). In a

recent study, we showed that Unified Segmentation with Cost Function Masking (CFM) yielded accurate registrations in adult patients with chronic stroke (Ripolles et al., 2012). Therefore, Unified Segmentation with medium regularization and CFM was applied to the T1-w using the resliced lesion mask, in order to obtain the normalization parameters (Andersen et al., 2010; Brett et al., 2001; Ripolles et al., 2012). Then, using these parameters, both the T1-w and the resliced lesion mask were normalized to MNI space. FSL FNIRT (FMRIB's Nonlinear Image Registration Tool; Jenkinson et al., 2012) is, another registration algorithm that, as Unified Segmentation, computes non-linear registration using linear combinations of splines (having around 30.000 degrees of freedom; Klein et al., 2009), although it does not use a set of tissue probability maps to calculate the registration parameters. FNIRT has been shown to produce very accurate registrations when compared to other normalization methods in healthy participants (outperforming those of Unified Segmentation, see Klein et al., 2009). Thus, we also used FSL's FNIRT to register the patient's T1-w and the lesion map, that was already registered to the space of the pediatric, age-appropriate (3-year-old) brain template from the Neurodevelopmental MRI Database (see above, the methods section for lesion characterization; Almlil et al., 2007; Fillmore et al., 2015; Richards et al., 2015; Sanchez et al., 2011), to the MNI152 adult one. In particular, we first linearly registered the patient's T1-w and lesion map to the MNI152 using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson et al., 2012). Then we used FNIRT to non-linearly register the patient's images to the adult template. For all these steps, CFM was also used. We then fed separately the two different normalized lesion maps to Tractotron to obtain the percentage of likelihood for the different segments of the AF to be affected by the lesion.

f. Localization of the lesion with respect to « classic language areas »

In order to assess the extent of overlap between the lesion and classically observed language-related areas, we completed two additional analyses. Firstly, we performed a meta-analysis using NeuroSynth (a platform for large-scale, automated meta-analysis of fMRI data; www.neurosynth.org; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). We calculated a term-based search on language that resulted in 885 studies (search performed on October 23, 2015). Then, a reverse inference map was generated. This reverse inference map depicts the brain regions that are preferentially related to the term language. We chose this option instead of a forward inference map (which displays brain areas that are consistently active in studies which highly load on the term language), because several brain regions are consistently reported in different kinds of studies (Yarkoni et al., 2011). Thus, a reverse inference map is much more informative than a forward one, as it shows areas which are more diagnostic of the term language, instead of brain regions that are just activated in studies associated with that term. Then we used FNIRT to register the reverse inference map (which was in MNI space) to the 3-year-old template space from the Neurodevelopmental MRI Database. Once in the same template space, cortical fMRI language-related activations were compared with the lesion location.

Secondly, we also obtained, from Smith et al., (2009), a resting state left fronto-parietal network (from a set of resting state networks that showed highly correspondence between resting and activation brain dynamics). This network is supposed to be strongly related to language paradigms (Smith et al., 2009; Lopez-Barroso et al., 2015). Following the same procedure as with the NeuroSynth meta-analysis, we registered this network (which was in MNI space) to the 3-year-old template using FNIRT. Again, once in the same template space, the location of the lesion regarding the language-related resting state network was compared.

g. fMRI experimental design

For the language task, we used a spontaneous narration of a short children story (The snowman by Raymond Briggs) recorded in child-directed speech by a female native Spanish speaker. The story was divided in ten blocks of 20 sec, each block containing short sentences forming a sequence of complete intonation phrases.

The ten blocks containing the original story (Language condition) were presented in order, with 15 sec rest periods between blocks where no stimuli were presented (Rest condition). The off-resting periods were set to 15 sec because the BOLD response in children returns to baseline levels faster than in adults (see Richter and Richter, 2003; Blasi et al., 2011).

h. fMRI preprocessing and statistical analyses

Data were pre-processed using Statistical Parameter Mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, University College, London, UK, www.fil.ion.ucl.ac.uk/spm/). All the analyses were done in native space. The main functional run was first realigned and then spatially smoothed with an 8 mm FWHM kernel.

A blocked-design matrix was specified using the canonical hemodynamic response function. Two different conditions were specified: Language and Rest. Data were high-pass filtered (to a maximum of 1/128 Hz) and serial autocorrelations were estimated using an autoregressive [AR(1)] model. Remaining motion effects were minimized by also including the estimated movement parameters in the model. A Language > Rest contrast was calculated. Unless otherwise noted, all statistics are reported at an uncorrected threshold of $p < .01$ at the voxel level with a minimal cluster size of 10 voxels (492 mm³).

i. resting state functional connectivity analysis

For the resting state data, the same pre-processing as for the fMRI task was implemented. Then, using GIFT (<http://icatb.sourceforge.net/>), Independent Component Analysis (ICA) was used to extract different networks representing the intrinsic functional connectivity of the resting state session. ICA was applied with the number of independent components set to 20, which has been shown to be a good dimension in previous studies (Forn et al., 2013; Smith et al., 2009). Processing started with an intensity normalization step. Then, data were first concatenated and then reduced to 20 temporal dimensions (using principal component analysis), to be then analyzed with the infomax algorithm (Bell & Sejnowski, 1995). Empirical z-thresholding was used on the resulting networks, using a threshold of $p < .01$ with 10 voxels (492 mm³). Analyses were repeated extracting 15 and 25 resting state networks and still no left FTN was retrieved; however the right FTN was still present in all cases.

j. DW-MRI pre-processing

Diffusion data processing started by correcting for eddy current distortions and head motion using FMRIB's Diffusion Toolbox (FDT), which is part of the FMRIB Software Library

(FSL 5.0.1, www.fmrib.ox.ac.uk/fsl/; Jenkinson et al., 2012). Subsequently, the gradient matrix was rotated (Leemans & Jones, 2009). Following this, brain extraction was performed using the Brain Extraction Tool (Smith et al., 2006), which is also part of the FSL distribution.

Fiber orientation distributions (FOD) were reconstructed using a spherical deconvolution approach based on the damped version of the Richardson-Lucy algorithm (Dell'acqua et al., 2010) implemented in StarTrack software (<http://www.natbrainlab.com/>). We first visualized FOD fields in selected a-priori fiber crossing regions (isthmus/posterior body of the Corpus Callosum and Corona Radiata). We then selected a combination of Spherical Deconvolution parameters that nicely resolved crossing, and at the same time avoided spurious peaks in GM or CSF (a fixed fiber response corresponding to a shape factor of $\alpha = 2 \times 10^3 \text{ mm}^2/\text{sec}$; 200 algorithm iterations, regularization threshold $\eta = .04$ and regularization geometric parameter $\nu = 8$). In order to discriminate between true fiber orientation and spurious components, we applied a double threshold approach (.1 absolute threshold and 10% relative threshold of the maxima amplitude of the FOD). The tractography was then conducted using an Euler algorithm with 1 mm step size with a fractional anisotropy (FA) threshold of .2 and an angle threshold of 35. These parameters were established based on our data set suitability and in comparison with previous studies (Catani et al., 2012; Dell'acqua et al., 2010; Vergani et al., 2014).

k. Deterministic tractography

The three segments of AF were defined following the procedure reported by Catani et al. (2007) and also used in Lopez-Barroso et al. (2013) and Tuomiranta et al. (2014). A region of interest (ROI) approach and TrackVis software were used (www.trackvis.org, Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). All ROIs were defined using the FA or RGB FA map as a reference (see Fig. 2A for ROIs location). These FA and RGB-FA maps were generated from diffusion tensors that were reconstructed using the linear least-squares method provided in Diffusion Toolkit (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). The ROI for the frontal area was placed in the coronal plane, between the central fissure and the cortical projection of the tract (green on the color-coded map). The ROI for the temporal area was placed in the axial plane encompassing the fibers descending to the posterior temporal lobe through the posterior portion of the temporal stem (blue in the color-coded map). The third two-dimensional ROI was defined at the sagittal plane encompassing the angular and supramarginal gyri of the inferior parietal lobe.

In order to virtually dissect the three segments of interest, different two-ROIs combinations were applied. The streamlines going through the frontal and temporal ROIs were classified as the long segment of the AF (red color in Fig. 2A); the streamlines connecting the temporal and parietal ROIs constituted the posterior segment of AF (yellow in Fig. 2A); and the streamlines passing through the frontal and parietal ROIs formed the anterior segment of the AF (green in Fig. 2A). This process was carried out for both the left and the right hemisphere. Since not only dorsal, but also ventral white matter pathways can contribute to language comprehension and learning, we also performed virtual in vivo dissections of the inferior IFOF, ILF and UF. These dissections were performed for both hemispheres to ensure that none of these tracks were affected by the lesion. We placed three spherical ROIs at the level of the anterior temporal lobe (temporal ROI), the posterior region located between the occipital and temporal lobe (occipital ROI) and the anterior floor of the external/extreme

capsule (frontal ROI). In order to define each of the tracts of interest we applied a two-ROI approach. The ILF was obtained by connecting the temporal and occipital ROIs. The streamlines passing through the occipital lobe and frontal ROIs were considered as part of the IFOF (blue). The frontal capsule ROI was united to the temporal ROI to delineate the UF (orange). All these ROIs were applied according to anatomical landmarks defined in the research report by Catani and Thiebaut de Schotten (2008). These processes were carried out for both the left and the right hemisphere.

4. Results

a. Neuropsychological testing

i. Bayley scales of infant and toddler development (BSID-III)

Results from the assessment performed at 25 and again at 42 months of age are presented in Table 2. While the scores in each of the three main subscales (Cognitive, Motor and Language) at age two years fell totally within the average range, the reassessment at 3½ years revealed lower levels of attainment. Cognitive and motor scores fell at the low end of the average range, but most critically, language showed the lowest score, almost below average, corresponding to a percentile value of 18. Both expressive and receptive domains were affected, but the former lagging slightly behind the latter (1 point). A closer look at the answers obtained during testing revealed that the patient failed at producing contingent utterances expanding previous productions from the experimenter, at correctly describing actions from pictures and at answering to what and where questions and to questions requiring logical answers related to functions. The patient was unable to consistently use plurals and did not produce prepositions or locative adverbs, utterances being still limited to two word combinations. Even the simplest, present progressive verb form was not always produced in his spontaneous speech. In receptive language items he failed at identifying elements involving prepositions and locative adverbs, colors, pronouns, plurals, comparatives and verbal tenses (past and future).

ii. Peabody vocabulary test

Results from the standardized receptive vocabulary test (PPVT-III, with Spanish norms), indicated that the patient's score (a raw score of 24) corresponded to a verbal IQ of 95 (percentile 37) equivalent to a developmental age of 3 years 2 months. The score in this test was totally within normal range. Recall that the test only requires pointing to one picture, from an array of four, representing nouns, verbs and adjectives (only one is included in the items for age 4 years). He was correct on all 12 items for age level 2.5 e 3 years and failed 3 of the twelve items of the subset for the next age level (4 years). These results are clearly in contrast with results from the receptive subscales in BSID-III, but it has to be noted that PPVT is limited to vocabulary knowledge of content words and it does not assess receptive knowledge of function words and grammar (locative, comparatives, noun and verb morphology) which were clearly underdeveloped in this child.

iii. Phonological development

Before reporting on the data, it must be noted that most of the thirty-two target words from the assessment tool for phonological development had to be elicited using a differed

imitation strategy, as the patient had limited capacity to spontaneously describe the images using complete sentences (see next section for details on spontaneous sentence production). For instance, to elicit the target word “jacket”, he was requested to answer the following question about the boy in the picture: “is he wearing a jacket or a coat?” Asking for an immediate repetition of the target word was maximally avoided and only used when no answer could be obtained. Qualitative analysis of the words produced in terms of the segments correctly and incorrectly produced and the phonological simplification processes present in his rendition of the target words indicate that the patient's phonological level is compatible with the characteristics of a delayed or protracted phonological development. He was able to produce most of the consonantal segments, except for the fricative and affricate sounds /q/ and /tʃ/, and he also had trouble in consistently producing the contrastive /l/ /r/ /d/ sounds. But besides those rather frequent errors in 3- to 4-year-old children, the patient had problems in correctly producing different syllabic structures beyond the simple CV, omitting all coda consonants in CVC end of word structures, and still simplifying some, but not all, complex CCV onsets and diphthongs in syllabic nuclei.

Assimilation processes (i.e., substituting one consonant for a segment present in a different syllable of the same word) were not infrequent. Overall, his phonological profile was closer to one from a younger child rather than to a profile of a phonological disorder. Quantitative measures of whole-word complexity (pMLU) and proximity to the adult rendition of the target words were obtained, following Ingram (2002) and also Hase, Ingram, and Bunta (2010). Phonological MLU score was 6.94 and Proximity score was .84. Compared to the values from the reference group (N = 50) of the same chronological age (pMLU score: 7.55, SD .55; Proximity score: .91, SD .06), the patient's score was below 1 SD from the mean score of the group (see Fig. 3). Taken together, both the qualitative and quantitative analyses converged: a delayed or protracted phonological development was revealed, as scores were located at the low end of the average measures for this age range.

iv. Utterance complexity in spontaneous speech

From the recordings of the language assessment session, a total of fifty-five spontaneous utterances could be entered into the analysis of MLU in words. Excluded were unintelligible utterances, repetitions, yes/no answers and also expressions in short answers such as ok, don't know, and social routines. Mean MLU in words was 2.8 (SD 1.3). Values from the reference group were 3.5 (SD .57), so the patient was found to be below 1 SD of the mean in that group. The mean value of the MLU of the patient's five longest utterances (max-L) was 5.8 and the value from the reference group was 9.07 (SD 2), the difference being closer to two SD for this measure. The longest utterances produced by the patient were still simple in terms of their noun and verb phrase components. When verbs were produced, errors in subject-verb agreement were present in his longer utterances. These important limitations in spontaneous expressive language were corroborated when the “Sentence Repetition” subtest of the NEPSI-II was administered. He reached a score of 6, while the average score is 10 with a SD of 3, failing to correctly repeat sentences such as “the dog ran fast” [El perro corrió a de prisa] or “Mary played with the ball” [Maria jugaba a la pelota] omitting at least one element.

Overall, expressive language in this patient was below standard levels at age 3.5 years, both in terms of phonological complexity at word level, but most importantly, in morphological and syntactic complexity at sentence production level.

v. Word learning skills (Fast-mapping and recall task)

Control group mean scores for the immediate recall and delayed recall were: 6.4 (SD = 1.26, median = 6.5) and 5.90 (SD = .88, median = 6.0), respectively. Mean number of novel words learned was 2.8 (SD = .92, median = 3) in the immediate recall and 2.5 (SD = .53, median = 2.5) in the delayed recall phase. Even though the task involved the learning of just four different words, data from the control group revealed that while the initial step of word learning via fast mapping was easily achieved (mean = 3.7, SD = .4; median 4; with only three out of ten participants making one wrong object selection), retention of the four novel word-referent associations was not straightforward, as seen from the immediate and delayed recall scores just reported.

The patient successfully pointed to the target novel objects in the mapping phase, with no error (see Fig. 4). The level of performance was not significantly different from the control group: control group (m = 92.5% of correctly mapped; SD = 12.08) versus patient (100%; Crawford test, one tailed, $t = .59$; $p = .28$). However, there were significant differences between the patient and the control group when comparing the level of performance in the recall phases. In immediate recall, the patient showed significantly lower abilities than the control group in both types of measures, scoring 1 out of eight when measuring total number of trials with correct object selection and scoring 0 regarding the number of object-referent mappings consistently selected in both trials. Comparisons based on 8 trials: Control group (m = 6.4; SD = 1.26) versus patient (1) [Crawford test, one tailed: $t = 4.09$; $p = .001$]. Comparisons based on the number of number of objects correctly recalled in both trials: Control group (m = 2.8; SD = .92) versus patient (0) [Crawford test, one tailed, $t = 2.9$; $p = .009$].

The results from the delayed recall phase, again considering both types of measures, were the following. Comparisons based on 8 trials: Control group (m = 5.9; SD = .88) versus patient (1) [Crawford test, one tailed: $t = 5.31$; $p < .001$]. Comparisons based on the number of number of objects correctly recalled in both trials: Control group (m = 2.5; SD = .53) versus patient (0). [Crawford test, one tailed, $t = 4.49$; $p = .001$]. Again, the patient showed significantly lower delayed recall abilities than the control group.

Correct selection trials in immediate and delayed recall (one hit in each case) did not correspond to the same object, so the initial ability to fast map the label to the novel object in this task had left no trace to be recovered that could help succeed in the recall phases. The patient showed instead an unexpected behavior, which consisted in pointing to the familiar object, thus avoiding the selection between the two novel objects, the target and the competitor. Only one child in the control group made once a similar wrong selection, limited to one of the novel objects in the recall phases.

b. Neuroimaging results

i. Lesion location

According to the 3-year-old adapted LONI LPBA40 brain atlas included in the Neurodevelopmental MRI Database (Richards et al., 2015; Shattuck et al., 2008), the lesion affected the left insula, left precentral, postcentral, superior parietal and supramarginal gyri and small portions of the middle-posterior part of the superior temporal gyrus (including the planum polare, temporale and Heschl's gyrus). The lesion did not overlap at any point with the inferior frontal gyrus. The analysis of the extent of the lesion revealed that WM volume loss in the left hemisphere almost doubled that of GM (8.47% WM loss and 4.8% GM loss in

the left hemisphere, compared to the right). This suggests that the lesion affected mainly white matter tissue.

ii. Track-wise lesion-deficit analysis

The track-wise lesion analysis, carried out independently from the in vivo dissections of the AF, provided additional and complementary evidence suggesting that the patient had the three segments of the left AF affected. Specifically, using the normalized lesion map obtained with Unified Segmentation, we obtained a 100% probability of disconnection for the long and anterior segments of the left AF and an 83% probability of disconnection for the left posterior segment. Using the lesion map yielded by FNIRT, the results were almost identical: 100% probability of disconnection for the anterior and long segments of the left AF and 88% for the left posterior segment. Fig. 5 shows the overlap in MNI space between the lesion mask (Using Unified Segmentation) and the three different segments of the left AF from the Tractotron atlas (Thibeaut de Schotten et al., 2011).

iii. Localization of the lesion with respect to “classic” language areas

The NeuroSynth meta-analysis revealed that there was only a small overlap at the superior temporal gyrus between general language-related activations and the patient's lesion (see Fig. 6A). Regarding the language-related resting state network, we only found a small overlap with the lesion at the supra-marginal gyrus (see Fig. 6B). Taking into account that the track-wise lesion analysis yielded a 100% probability of disconnection of the left AF and that the WM loss almost doubled that of GM, these results further suggest that the lesion had little effect on cortical areas classically related to language, while clearly impacting the left dorsal white matter pathways.

iv. fMRI language task

The Language versus Rest contrast yielded activations in the right middle and superior temporal gyrus, the right angular gyrus and the left cerebellum (see Table 3 and Fig. 7A). There was an overlap between the right supramarginal/angular cluster of this contrast and the right lateralized temporo-frontal network found for the resting state (see resting state results and overlap, Fig. 7B and C and Table 4).

v. Resting state analysis

A right lateralized fronto-temporal network (rFTN) that covered the right superior temporal, supramarginal and inferior frontal gyri (see Fig. 7B) was observed. Interestingly, no mirror left-lateralized FTN was found. Analyses were repeated extracting 15 and 25 resting state networks and still no left FTN was retrieved; however the right FTN was still present in all cases. There was an overlap in the right superior temporal gyrus between the activation from the fMRI Language > Rest contrast and the right FTN (see Fig. 7C; see also Fig. 2B for an overlap with the right arcuate fasciculus), thus providing convergence results for our fMRI data. In their seminal study, Smith et al., (2009) described several major brain networks which showed high correspondence between resting and activation brain dynamics. Here, we found very similar networks to those described by Smith et al., (2009) except for the left fronto-

temporal and the cerebellar network (although some networks included portions of the cerebellum, none covered the entire structure). However, the fact that the network covering the cerebellum is missing should not come as a surprise as, due to reduced field of view, the most inferior part of this structure was not acquired during MRI scanning (which is a common issue, Smith et al., 2009). The following canonical resting state canonical networks (Smith et al., 2009) were also identified (see Fig. 7D): a default mode network, an auditory network (covering the superior temporal gyrus bilaterally), several visual networks, a sensori-motor network (covering the precentral and post-central gyri bilaterally and the supplementary motor area) and an executive control network (including medial-frontal areas and the anterior and middle cingulate).

vi. Deterministic tractography

The deterministic *in vivo* dissections using the two-ROIs approach revealed that all three segments of the AF were well preserved in the right hemisphere. Meanwhile, we were not able to dissect the long segment of the left AF. In addition, only few streamlines of the anterior segment were detectable, while the posterior part of the left AF was more preserved. First, we performed a one-ROI approach for the frontal and temporal ROIs separately, which permitted us to explore all the fibers that passed through each area. We detected several streamlines, presumably part of the remnants of the left long segment of the AF, departing from the temporal ROI and reaching the lesioned area (red circle in Fig. 2A). We also detected the same pattern of streamlines exiting the left frontal ROIs and stopping at the lesioned area. We also placed an additional 7.5 mm sphere around this area of disconnection. With this new “disconnection area” (DA) ROI we performed the two ROI approach again, tracking all the fibers departing the left frontal ROI and reaching the DA. The process was repeated for the streamlines exiting the temporal ROI and arriving to de DA. We then found two parts of the disrupted left long segment of the AF (see Fig. 2A, red streamlines in the left hemisphere). Bearing in mind that also the ventral white matter pathways (ILF, IFOF and UF) are widely considered as associated with language processing (Hickok & Poeppel, 2007; Rauschecker, 2012; Saur et al., 2008; Weiller et al., 2011) we performed virtual *in vivo* dissections also for these tracts. We did not observe any substantial damage or discontinuity for the tracts of interest on either hemisphere (see Fig. 2C).

5. Discussion

In the present article we report the results of a multi-methodological approach to study a 3.5-year-old boy, born at term with a perinatal ischemic stroke of the left middle cerebral artery, affecting mainly the supramarginal and parietal gyri, the insular cortex the precentral and postcentral gyri and small portions of the superior temporal gyrus. We evaluated the child for cognitive, motor and linguistic abilities at 2 and 3.5 years of age. At the latter age, word-learning abilities were also assessed using a fast-mapping and recall tasks adapted for pre-schoolers (3-4 years). We found that only the receptive vocabulary score from the PPVT-III fell within normal limits. While language scores from the BSID-III, at 2 years of age were still within average, they fell at the very low end of the normal distribution by 42 months of age, when more sophisticated lexical, conceptual and grammatical knowledge is expected to have already been acquired. Finally, at this age, functional and structural imaging data as well as a measure of intrinsic functional connectivity were acquired under propofol. The

precise lesion location and characterization suggested that (i) the lesion is unlikely to affect classic language cortical areas and (ii) the lesion affects mainly the left dorsal white matter tracts. In addition, our results point towards functional and structural brain reorganization effects induced by the perinatal stroke that are likely to explain the language performance observed. Notably, the two types of analyses evaluating the integrity of the dorsal and ventral pathways showed converging evidence of an affected left AF with a possible disconnection of its long and anterior segments. Moreover, both functional activations during a passive-listening task and a resting-state session pointed toward a right lateralized language network.

Firstly, in terms of functional activations, the presentation of sentences induced a rightward activation in the right middle and superior temporal gyrus and in the right angular gyrus, known to be implicated in lexical-semantic processing in healthy adults (Binder et al., 1997; Demonet, Price, Wise, & Frackowiak, 1994). However, no activation was found over the left hemisphere (see Fig. 7, Language vs Rest contrast). These findings on speech perception extend previous results on speech production, which showed that patients with left hemisphere stroke recruiting additional left-brain regions have better language functions than those who largely recruited right-hemispheric brain areas (Raja-Beharelle et al., 2010). Moreover, increased posterior superior temporal gyrus inter-hemispheric functional connectivity during an audio-visual story listening task predicted better language performance in a group of 7- to 29-year-old patients with perinatal stroke, but worse performance in typically developing controls, suggesting that modifications of inter-hemispheric functional connectivity may be a compensatory mechanism after early stroke (Dick et al., 2013). The resting state analysis converged with our fMRI results as we found a fronto-temporal network (FTN) covering the right superior temporal and inferior frontal gyri (see Fig. 7B). Importantly, the fMRI language contrast and the right FTN showed an overlap in the right superior temporal gyrus (see Fig. 7C; for comparison with the intact right-hemispheric arcuate see Fig. 2B). While this network is generally left lateralized in adult and child healthy controls (Greicius et al., 2008; Kiviniemi, Kantola, Jauhiainen, Hyvarinen, & Tervonen, 2008), our patient showed a right lateralized pattern. Despite recent evidence showing that different levels of propofol can impact the identification of resting state networks in macaque monkeys (Barttfeld et al., 2015), we found several typical brain networks such as the canonical default mode, auditory, visual, executive and sensory-motor networks which were intrinsically connected during rest (see Fig. 7D). These functionally connected networks were very similar to those found in healthy adults despite anesthesia (Smith et al., 2009). Taken together, the functional activations converge in showing a right lateralized brain network both during a passive listening task and during rest. Thus, the idea that better language outcome after early left hemisphere injury relies on the contribution of the non-affected right hemisphere (Lidzba & Staudt, 2008; Rasmussen & Milner, 1977) should be cautiously considered.

Secondly, the combined patterns of structural and behavioral data are interesting in the framework of the SCALED model (Catani & Bambini, 2014). Deterministic tractography revealed a very unusual shape in the left AF, suggesting that both the anterior and long segments of the AF were affected by the lesion (see Fig. 2). Importantly, the right AF and the bilateral ventral tracks appeared to be unaffected and thus were successfully reconstructed. Damage to the left AF was further explored with a lesion analysis which showed, again, that the lesioned area is mainly affecting the anterior and long segments of the left AF (see Fig. 5). While several studies have used DW-MRI to reconstruct the AF in adult patients with stroke (see for a review Jang, 2013) or in young children with cortical malformations (Paldino,

Hedges, Golriz, 2015; Paldino, Hedges, Gaab, et al., 2015), to our knowledge, no published data exist on the effect of left perinatal stroke on the integrity of both dorsal and ventral streams at such a young age. At the behavioral level, the patient had a normal comprehension but showed production impairment. Nonetheless, the patient failed at identifying elements involving prepositions and locative adverbs, colors, pronouns, plurals, comparatives and verbal tenses (past and future). To our knowledge, there is no study determining the white matter pathways underlying complex morpho-syntactic and verb-argument structures processing in children of this age but the intact language ventral streams found in our patient (UF, ILF and IFOF) might explain the relatively spared receptive vocabulary found in the PPVT-III. Indeed, these tracks connect brain regions in the temporal and frontal lobes that are thought to be crucial in the development of lexical and semantic processing (Brauer et al., 2013; Friederici, Kotz, Scott, & Obleser, 2010; Mesgarani et al., 2014). Moreover, Raettig, Frisch, Friederici, and Kotz (2010) have found in adult participants that morpho-syntactically ungrammatical sentences induced an increase of BOLD signal in the left superior temporal gyrus while verb-argument ungrammatical sentences elicited increased activation in the left inferior frontal gyrus.

In addition, our results add support to previous longitudinal findings in 18 patients with focal perinatal stroke (9 left and 9 right) showing a more delayed expressive vocabulary at 4 than at 2 years of age in the group of left perinatal stroke than in the right lesion group (Chilosi et al., 2001). While both receptive and expressive scores from the BSID-III were low, measures of phonological whole word production and utterance complexity in spontaneous speech confirmed that, our patient had clear difficulties in the productive aspects of language. This suggests a delay in the acquisition of complex phonological and morpho-syntactic structures. Specifically, the patient produced mainly short sentences, used simple syntactic structures, failed at basic noun and verb morphological rules and had poor phonological accuracy scores. This pattern of results has been already reported in previous studies in older children with perinatal stroke (Chapman et al., 2003; Demir et al., 2010; Reilly et al., 2013; Rowe et al., 2009) and is in line with studies showing an important role of the AF in the mapping between phonological information in the posterior temporal areas and motor information in the inferior frontal regions (Catani et al., 2005; Schmahmann et al., 2007). In this sense, the AF may serve as an interface between phonological input and articulatory representations (Hickok & Poeppel, 2007; Rodriguez-Fornells et al., 2009).

Furthermore, in addition of showing speech production deficits, the child was impaired in learning new word-referent associations, one of the milestones of language acquisition. Fast-mapping tasks considered to reflect crucial processes underlying vocabulary acquisition in early childhood (Bloom & Markson, 1998; Carey & Bartlett, 1978) were originally designed to specifically evaluate children's ability to associate novel word forms to unfamiliar objects. While no previous data exist in children who had a perinatal stroke, behavioral data suggest that typically developing 2-year-old pre-schoolers can recall at least one novel word-object association in an immediate recall condition (Spiegel & Halberda, 2011). Learning more than one word at a time is harder but supportive repetition or ostensive naming can induce successful learning (Axelsson, Churchley, & Horst, 2012; Axelsson & Horst, 2014). In our task children were required to learn four novel words from a single fast-mapping trial followed by some supportive strategies (two repetitions and one production of the target labels). At test, they were required to evaluate different label-object associations and to recognize specific phonological information to make the right selection of the target objects. Children's performance in this four-word learning task was thus not expected to be at ceiling, as

processing and retaining multiple noun-object mappings can be seen as a rather demanding activity. However, the patient only succeeded in one out of the eight test trials, whereas the control group was on average successful in six out of eight trials, both in the immediate and in the delayed recall conditions. Interestingly the different structural analyses performed with the DW-MRI and T1-w/FLAIR data converged in showing an affected long segment of the AF. The integrity of this fiber pathway from a cohort of adult participants predicted the level of performance in a novel word-learning task (Lopez-Barroso et al., 2013). Moreover, in healthy adult participants the posterior part of the left superior temporal gyrus and the left inferior parietal cortex have been associated to the ease of learning non-native phonological contrasts (Golestani, Paus, & Zatorre, 2002; Golestani, Molko, Dehaene, LeBihan, & Pallier, 2007) and phonological short-term memory during speech production (Henson, Burgess, & Frith, 2000; Keller, Carpenter, & Just, 2003; Martin, 2003). Thus, the pattern of results observed in our patient as well as those from previous studies strongly suggest that an impaired left lateralized speech network is accompanied by a range of language learning disabilities. This pattern of results provides clear evidence that patients with unilateral perinatal stroke can show impairment in language learning capacities (see also Lansing et al., 2004 for similar results in older children with pediatric stroke). Importantly, these data give further insight to the SCALED model proposed by Catani and Bambini (2014) by revealing cortical reorganization in the language network following left perinatal stroke and suggesting an important role of a functionally intact left hemisphere, especially of an intact AF, for the learning of novel word-referent associations, the building block of vocabulary acquisition.

From a methodological perspective, another important point of the present study is that we used a multi-modal neuroimaging protocol to thoroughly characterize the language network of the patient. We suggest that the use of different functional and structural analyses that provide convergent results can be advantageous to better understand the neural networks supporting language processing in a case study such as the one presented. Indeed, the study of the brain of a 3.5-year-old with perinatal stroke presents several difficulties related to both the age of the patient and the presence of a lesion. Firstly, in order to obtain useable data that are not affected by motion artefacts, the use of sedation is mandatory. While several studies have shown that it is possible to measure task-related fMRI activity under sedation, the rate of failure (no activation detected) can be as high as 21% when using propofol and an auditory task (Bernal et al., 2012). In this sense, resting state analysis provides another method to assess whether fronto-temporo-parietal networks, potentially related to language processing, are functionally connected. Regarding the structural analysis, we detected an affected left AF by using a deterministic approach that allowed us performing virtual *in vivo* dissections. In addition, and taking into account the limitations of our diffusion dataset, we used a track-wise lesion analysis that provided further evidence for an affected left AF (especially the anterior and long segments). It is important to note that this last approach, despite the methodological issues related to the normalization step, used information from the T1-w and FLAIR images, and thus produced results independent from the DW-MRI dataset acquired. Finally, the meta-analysis revealed that only a small portion of the superior temporal gyrus was overlapping with general language-related activations found in the literature. Therefore, we used different and complementary imaging techniques all providing convergent evidence for an affected left AF with relatively spared cortical language areas.

The present study presents some methodological limitations avoiding us to draw clear conclusions on the direct link between the integrity of the left anterior and long AF segments

and word learning abilities in the general population. Indeed, even though we report quantitative behavioural data tested against a group of matched control children, the neuroimaging data remain qualitative with some methodological limitations. It is also important to keep in mind that cognitive and linguistic data were collected at a very difficult age where only a handful set standardized test can be used. First of all, the spatial normalization of pediatric brain images to an adult template has several problems (Altaye et al., 2008). These include different GM and WM distribution between pediatric and adult brain templates, high variability of both local and global structural changes and misclassification of brain tissue (Sanchez et al., 2011; Richards et al., 2015). In the present study, both the track-wise lesion analysis and the overlap with the language/resting state general networks might suffer from these problems. Since the accuracy of normalization methods is highly variable (Klein et al., 2009), especially when dealing with lesioned brains (Ripolles et al., 2012), we decided to use two different normalization strategies to register our lesion map to the common MNI space. However and, in spite of the fact that in the track-wise lesion analysis both registration methods led to a 100% probability of disconnection for both the left anterior and long segments of the AF, we acknowledge that there might be a bias in these results, as in both cases an adult template was used. Nevertheless, we think that, notwithstanding the limitations of the track-wise lesion analysis, the fact that a 100% probability of disconnection was found, together with the deterministic tractography results, provide compelling evidence for an affected left AF in our patient. Second, although deterministic tractography has been widely used to assess the microstructural integrity of the AF after stroke in adult patients (Kim & Jang, 2013), this technique has also several limitations. In patients, the presence of degeneration, edema or necrosis can alter the microstructure of the tissue surrounding the lesion. This leads to difficulties in the estimation of fiber orientations, especially in areas with presence of crossing fibers, which can lead to artefacted track reconstructions (Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008; Dell'acqua et al., 2010; Møller et al., 2007; Schonberg, Pianka, Hendler, Pasternak, & Assaf, 2006). In addition, in severe stroke, the tractography of a particular track can be interrupted by the lesion (Borich, Wadden, & Boyd, 2012; Tang et al., 2010). To account for these problems, in our study we used a spherical deconvolution algorithm based on an adaptive regularization (damped version of the Richardson-Lucy algorithm), which has been shown to improve diffusion tractography in regions with multiple fiber-crossing (Dell'acqua et al., 2010). It has also been suggested that this algorithm has the potential to improve the reliability of the tract reconstructions in patient populations (Dell'acqua et al., 2010). Moreover, and, although we agree that in the present case the lesion did affect the track reconstruction, failure to successfully dissect a left AF has been shown to be a good marker of language dysfunction in both adult patients with stroke (Kim & Jang, 2013) and in a pediatric population with malformations of cortical development (Paldino, Hedges, Golriz, 2015; Paldino, Hedges, Gaab, et al., 2015).

Conclusion

The present case study is important due to several reasons. To our knowledge, no previous studies have provided a 3D reconstruction of the dorsal and ventral language pathways in a young child who had a left perinatal stroke. By showing that a damaged left AF with relatively spared cortical language areas can impair word-learning abilities, these results refine the observation (already present in recent research, as in Fuentes et al., 2014) that children who had stroke affecting crucial language areas, including white-matter pathways of the left hemisphere, are especially vulnerable to the negative impact of the stroke on their

later language outcomes. These results also add further support to the idea that children with perinatal stroke may “grow into” their deficits (Anderson et al., 2011; Dennis, 1989) and can present normal linguistic functions with new deficits that emerge over years, probably due to increasing demands relying on the connection of temporal and frontal language regions (Max, 2004). Cortical and subcortical maturation is known to be still at work well after 3.5 years of age (Friederici, 2012), thus, impaired language and word learning at 42 months of age in a patient with a relatively small lesion does not assure long-lasting deficits. Further longitudinal studies with larger number of participants and different types of lesions would help to solve this issue.

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Figures

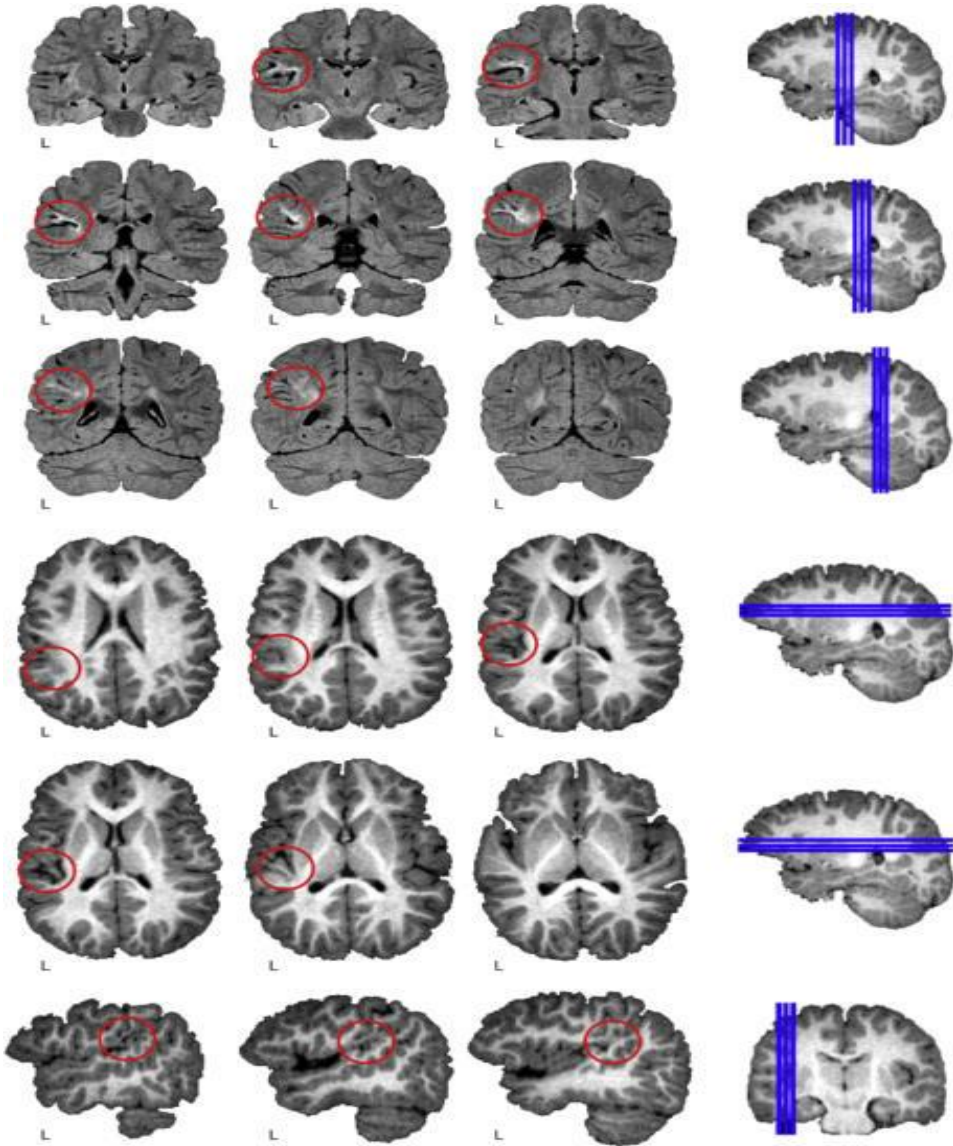


Fig. 1 Depiction of the left-hemispheric structural lesion in native space using a FLAIR image for coronal and a T1-weighted image for axial and sagittal slices. The lesion can be seen as an hyper-intensity in the FLAIR and hypo-intense areas in the T1-w image and is highlighted with a red circle. Neurological convention is used.

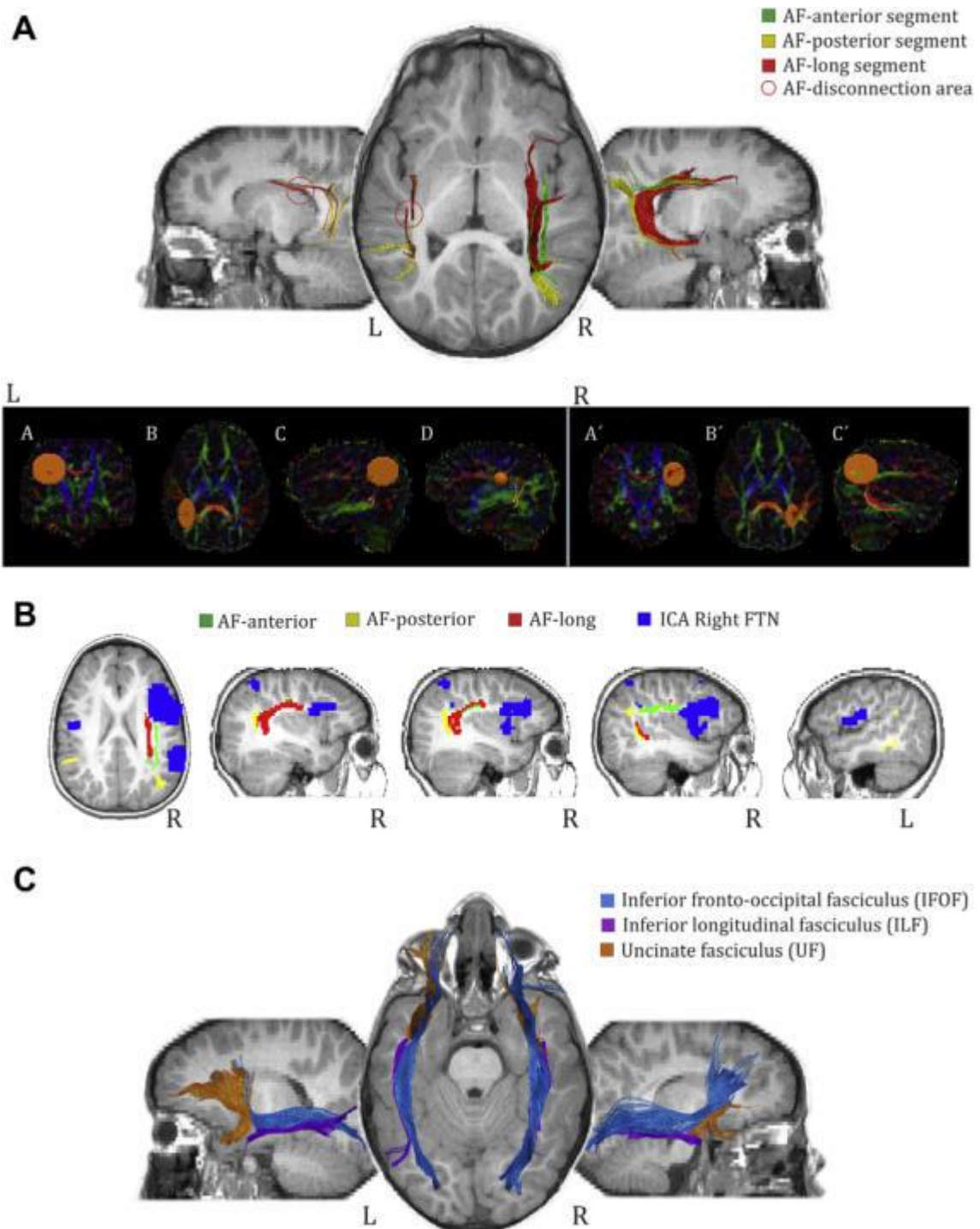


Fig. 2 Deterministic tractography. All results are shown in native space. Neurological convention is used. A. Upper part: in vivo dissections of the left and right AF depicted on the sagittal and axial planes. For the left hemisphere the two disconnected parts of the left long segment of the AF are shown (see Results). Lower part: ROI placements depicted on the color RGB maps: A and A' e frontal ROIs, B and B' temporal ROIs, C and C' e parietal ROIs, D-left hemisphere "disconnection area". B. Overlap between the three segments of the right arcuate fasciculus, the posterior segment of the left AF and the right fronto-parietal resting state network. C. In vivo dissections of the left and right IFOF, UF and ILF depicted on the sagittal, transversal and axial planes. The three fiber tracks were correctly reconstructed in both hemispheres (see Results).

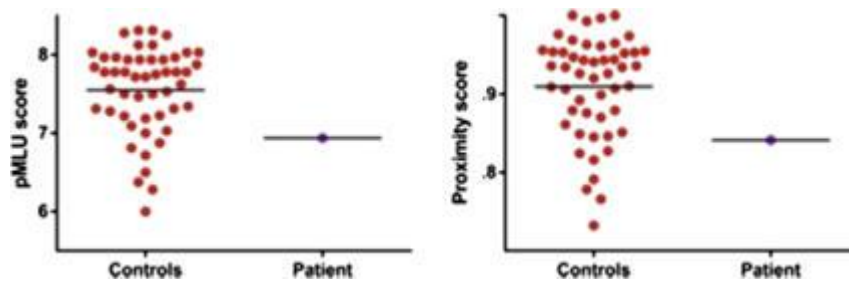


Fig. 3. Phonological MLU (pMLU) and Proximity scores from the phonological assessment. The graphs represent individual scores for the pMLU scores (left) and Proximity score (right) from the referent group N = 50 (empty symbols), the group mean value (in bold) and the score from the patient (red circle). [Maximum score for the pMLU score (complexity of the segmental structure of the words (consonants) is 8.31); maximum score for Proximity score is 1].

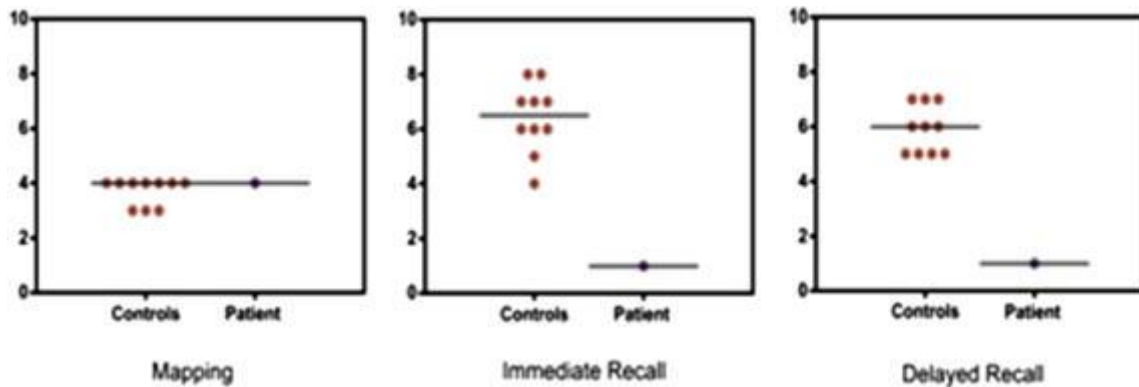


Fig. 4. Fast Mapping and Recall Tasks. The graphs represent the individual scores for the control group matched in age (N = 10) and the patient in the three phases of the task. The first graph on the left depicts the level of performance in the mapping phase. Note that the patient was able to perform this task. The graph in the middle depicts the level of performance in the immediate recall phase while the third graph on the right depicts the level of performance in the delayed recall phase. Note that in both the immediate and the delayed recall phases the patient was able to recall only one new object.

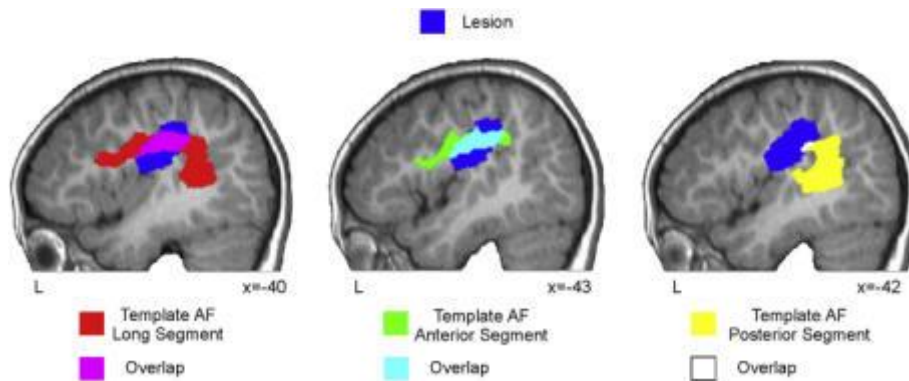


Fig. 5. Track-wise lesion analysis. Overlap between the different segments of the AF and the lesion mask. The lesion mask is depicted in dark blue. Probability templates for the long (in red, overlap with the lesion in pink), anterior (in green, overlap with the lesion in light blue) and posterior (yellow, overlap with the lesion in white) segments of the AF were extracted from the Tractotron atlas (Thibeaut de Schotten et al., 2011) and are thresholded at a 50% (only voxels having a 50% probability of being part of the AF according to the atlas are shown). Results are overlaid over the T1-w image in MNI space, with coordinates at the bottom right of each slice. Neurological convention is used. L, left hemisphere; R, right hemisphere; AF, arcuate fasciculus.

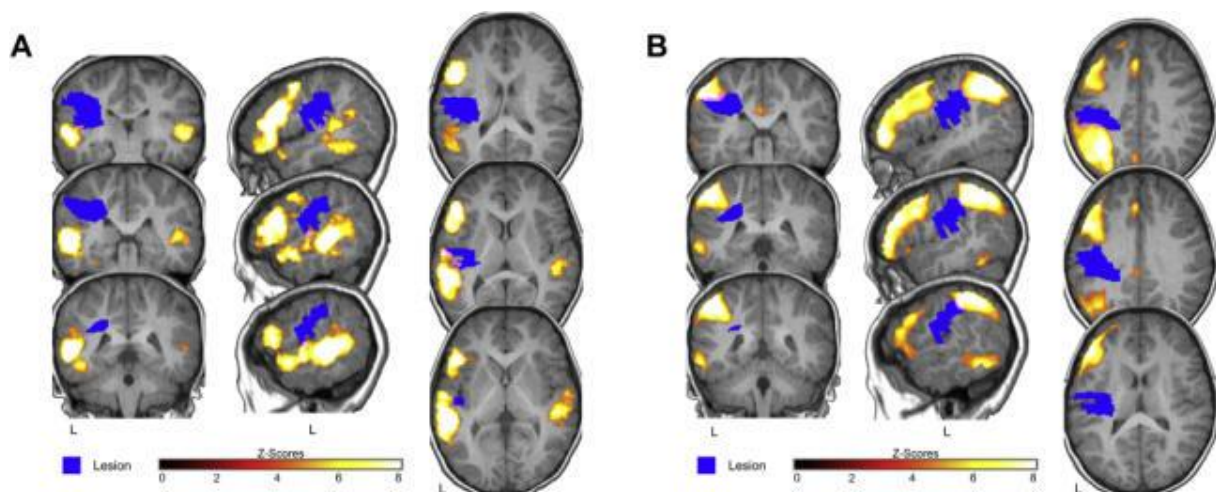


Fig. 6. Comparison with classical language-related cortical areas. The lesion is shown in blue over the patient's T1-w registered to the Neurodevelopmental MRI Database 3-year-old template. In red-yellow, thresholded at $z = 4$, results for A) the NeuroSynth fMRI meta-analysis on the term language and B) the language-related resting state network from Smith et al., (2009) are shown. Note that there is only a small overlap (in pink) at the left superior temporal gyrus and at the left supramarginal gyrus between the lesion map and images A and B, respectively.

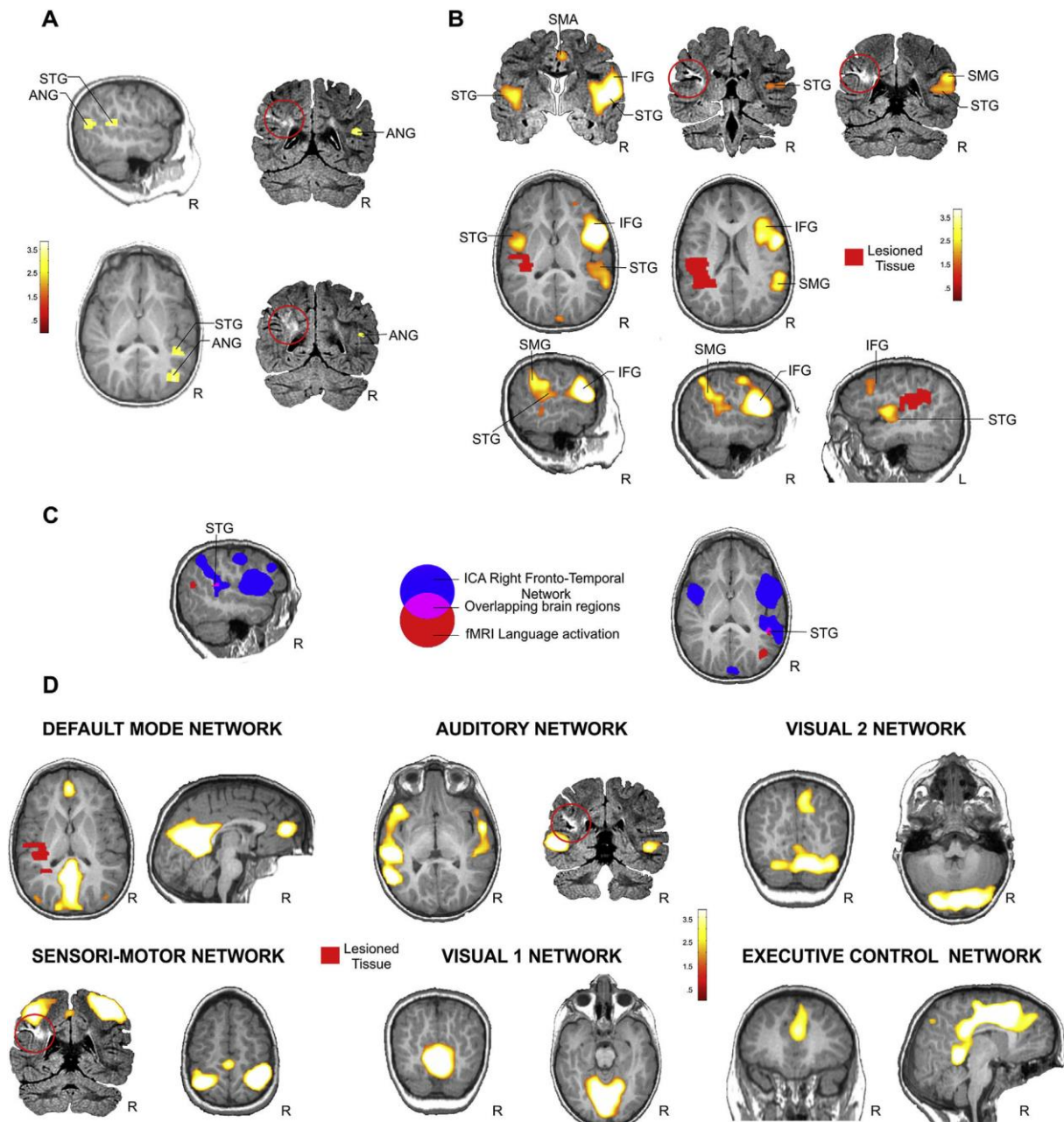


Fig. 7. Results are shown, in red-yellow and at a $p < .01$ uncorrected threshold with 10 voxels of cluster extent, in native space over the patient's T1-w or FLAIR image. The lesion can be seen as a hyper-intensity in the FLAIR image (highlighted with a red circle) or with a red lesion map when shown over the T1-w. Neurological convention is used. A. Enhanced fMRI activity for the Language versus Rest contrast. B. Resting state right lateralized Fronto-Temporal Network. C. Overlap at the right superior temporal gyrus (pink) between the fMRI activation for the Language versus Rest contrast (red) and the right lateralized Fronto-Temporal network from the resting state (blue). D. Other classical resting state networks retrieved. Right Hemisphere; L, Left Hemisphere; STG, Superior Temporal Gyrus; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SMG, Supramarginal gyrus; ANG, Angular Gyrus; STG, Superior Temporal Gyrus.

Table 1. Summary of the different behavioral tests administered at two different age levels in the patient and in the corresponding control group.

Age at test	Test, assessment tool	Domain	Reference values (mean, SD)
25 months	Bayley Scales of Infant and Toddler Development (BSID-III)	Motor, cognitive and language scales	Scaled scores (10, 3) Composite scores (100, 15)
42 months	Bayley Scales of Infant and Toddler Development (BSID-III)	Motor, cognitive and language scales	Scaled scores (10, 3) Composite scores (100, 15)
	Peabody Picture Vocabulary Test (PPVT-III)	Receptive vocabulary	Verbal IQ (100, 15)
	Test of phonological assessment (Bosch, 2004)	Phonological development	Rank percentile & developmental age Qualitative developmental profile, 3 levels Quantitative whole-word production measures N = 50, from 3; 00 to 3; 11 (years; months) Phonological Mean Length of Utterance (pMLU) and whole-word proximity score pMLU: (.755; .55); proximity score: (.91; .064) Mean Length of Utterance in words (MLU) & Mean MLU for the five longest utterances (max-L) N = 50, at 3; 06 (years; months); Age, educational level and language matched group from Fernandez & Aguado (2007) MLU in words: (3.5; .57) Mean max-L: (9.07; 2)
	Free play and conversational setting	Spontaneous expressive language complexity	Reference age-matched group N = 10; similar language, background and parents' educational level; mean % correct trials (out of 8 requests): immediate recall: (6.4; 1.26); delayed recall: (5.9; .88) Mean % correct object selection (2 correct answers for each object): immediate recall: (2.8;.92); delayed recall: (2.5; .53)
	Multiple word-learning experimental task (adapted from Horst & Samuelson, 2008)	novel label-object mappings (4 objects) Immediate, delay recall	

Table 2. Summary of the scores from the Bayley scales of Infant and Toddler Development (Bayley-III) administered at two different age levels.

Scales	25 months				42 months						
	TRS	SC	CS	PR	TRS	SC	CS	PR			
Cognitive	61	9	95	37	72	8	90	25			
Motor	Fine motor	39	10	18	94	34	49	9	17	91	27
	Gross motor	53	8			68	8				
Language	Receptive	27	10	18	94	34	33	8	15	86	18
	Expressive	26	8			35	7				

Notes. TRS: Total raw score; SC: Scaled score; CS: Composite score; PR: Percentile rank.

Table 3. Anatomical areas showing enhanced fMRI activity for the Language > Rest contrast at a $p < .01$ uncorrected threshold with 10 voxels of cluster extent (see also Fig. 6).

Language > Rest		
Anatomical area	Size (mm ³)	t - value
Left cerebellum	1230	3.56
Right angular gyrus; Right superior temporal gyrus	1670	3.21
Right superior temporal gyrus	787	2.81

Table 4. Anatomical areas constituting the Right Lateralized Fronto-Temporal Resting

Right Lateralized fronto-temporal resting state network		
Anatomical area	Size (mm ³)	z - value
Right inferior frontal gyrus; right insula; right precentral gyrus	23,034	10.62
Right superior temporal gyrus; right supramarginal gyrus; right angular gyrus; right superior parietal gyrus	10,730	4.72
Left superior temporal gyrus; left insula	4035	3.89
Right cuneus	984	3.49
Left cerebellum	1230	3.30
Bilateral supplementary motor area	689	3.23
Left inferior frontal gyrus	935	2.91

p < .01 threshold with 10 voxels of cluster extent
(see also Fig. 7).