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Developments in diffusion MRI and tractography to study language network alterations following very preterm birth

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Abstract
Language is key for human interactions and relies on a well-known set of brain cortical areas linked by large-scale white-matter fasciculi. However, very little is known about the ontogeny of the language network, how it is affected by very preterm birth, or how structural connectivity profiles observable before language acquisition may predispose distinct computational mechanisms associated with later language processing. Recent advances in diffusion-weighted magnetic resonance imaging and tractography are allowing researchers to provide novel, insightful understanding of the human language brain network through in vivo non-invasive investigations across the whole lifespan. Here, we propose a commentary on a series of papers which aimed to summarise the latest technological advances in neuroimaging research in order to provide future directions to study language development following very preterm birth.

Keywords
diffusion magnetic resonance imaging, tractography, language, preterm
Background

Language represents one of the most important cornerstones of human evolution and its neural architecture arguably exemplifies it. The brain basis of language is believed to be a distinct piece of the biological makeup of our brain\(^1\)-\(^3\) and evidence regarding human neural specialisation for language has steadily accumulated during the last two decades\(^4\)-\(^6\). Nonetheless, key questions of broad scientific interest remain unanswered.

Today, non-invasive in vivo diffusion-weighted magnetic resonance imaging (MRI) represents a powerful tool with which neuroscientists are able to study the anatomical/structural architecture underlying the human brain’s ability to combine symbolic representation in rich and communicable systems of knowledge. Although to explain the physical basis underlying this technique is not within the aims of the present work\(^7\), diffusion MRI and tractography offer an important advantage over many other modalities: the possibility of highlighting the large-scale white-matter tracts underlying perisylvian cortical brain regions known as the human language network\(^8\). Diffusion MRI has found ubiquitous applications across the lifespan and has highlighted how the neural organisation of language processing can be further subdivided into ventral and dorsal streams. Each of these pathways consists of specific brain regions that are linked via distinct white matter bundles and that support diverse computational properties of language processing\(^9\)-\(^12\). Specifically, the ventral stream is organised into the inferior fronto-occipital and the uncinate fasciculi and is thought to be involved in the development of semantic processing\(^9\)-\(^12\), whilst the dorsal stream may underlie the development of core syntactic processing and is mainly characterised by the direct, long-distance branches of the arcuate fasciculi\(^13\)-\(^15\).

What diffusion MRI has taught us about typical and atypical development of the language system

Some of the most outstanding contributions to current knowledge about language development come from diffusion MRI studies investigating the ontogeny of the human brain language network\(^16\). These studies used cutting-edge methodology in infant populations, before the emergence of complex language abilities, to understand whether the human specialisation for language partially relies on a series of large-scale white-matter tracts which are present shortly after birth and which resemble the mature language network. These studies showed that infants’ vocalisation during the first six months of postnatal life might rely on the early development of the dorsal and ventral white-matter pathways and displayed some adult-like signs of microstructural specialisation and lateralization, which refers to the early microstructural differentiation of these language streams\(^16\). Recent work extended these findings, showing that in very preterm children, a population at well-known risk of long-lasting linguistic impairment, language and cognitive abilities at 20 months of postnatal age could be predicted by the microstructure of the adult-like bilateral arcuate fasciculus measured at the time of normal birth\(^16\). Measuring the tract microstructural organisation before the emergence of complex language may provide an early neural marker to potentially assess impaired trajectories of brain development of language-specific networks following very preterm birth. Furthermore, this result may represent a significant step towards understanding early human language brain specialisation, as it may show a precocious brain basis for the emergence of auditory-verbal working memory, which provides a buffer for language processing\(^17\)-\(^19\). Such an interpretation would be well aligned with the adult literature, showing the arcuate fasciculus is crucial for efficient auditory-verbal learning\(^20\)-\(^22\). Together, these studies and others\(^13\)-\(^23\) provide scholars with novel knowledge of typical and atypical developmental trajectories of the language system and may further aid the development of early, targeted interventions.

Other studies, though not directly investigating language abilities, have highlighted functional and structural brain alterations in very preterm adolescents\(^24\)-\(^31\). These could contribute to their risk of developing impaired linguistic function\(^32\)-\(^34\), even in the absence of brain injury or socio-economic deprivation, with long-lasting effects and increased need for speech therapy and educational support\(^35\). Mullen et al. studied very preterm adolescents, and reported that microstructure of the bilateral uncinate and arcuate fasciculi, respectively, was associated with scores on standardised tests of semantic and phonological abilities\(^36\). Northam et al. instead investigated specific neural correlates of language impairment in preterm adolescents, combining diffusion MRI and tractography with an in-depth language assessment\(^37\). Results showed that no inter-hemispheric tract was significantly associated with linguistic impairment. Instead, they found that a high proportion of variance in preterm adolescents’ linguistic abilities was explained by the integrity of inter-hemispheric connectivity, such as the anterior commissure and the temporal lobe inter-hemispheric fibres. These results provide evidence that, during later childhood, the long-lasting, complex language impairment seen in preterm born individuals\(^3\) may depend on the microstructure of inter-hemispheric associative bundles. However, we may speculate that this result could also be interpreted as a plastic mechanism of language reorganisation in childhood development, during which inter-hemispheric connectivity has a known early role in auditory processing\(^38\). In either case, these results point to the importance of inter-hemispheric connectivity and lateralization in language brain development following very preterm birth. Figure 1 summarises current hypotheses about impaired developmental trajectories of language-specific brain networks following very preterm birth.

Lessons from functional MRI

The idea that language brain organisation in very preterm samples may follow an adaptive developmental trajectory, in order to cope with broader high-order neurocognitive alterations in prefrontal areas, is not new, and it receives support from functional MRI studies (for example, 35). Scheinost et al. investigated whether functional lateralization may be associated with linguistic skills in preterm born individuals\(^39\),\(^40\). This work showed that young adults who were born very preterm presented alterations in functional lateralization compared with controls specifically in temporo-parietal junction and that greater
leftward lateralization was significantly correlated with more preserved linguistic abilities. Although directionality could not be inferred (that is, greater lateralization leads to better performance or the reverse occurs: better performance is driven by other mechanisms that are less impaired, which leads to greater lateralization), these results suggest that language functional lateralization could represent a marker of greater linguistic competence in preterm samples. We may further speculate that early behavioural interventions increasing cerebral lateralization of the temporo-parietal area could foster some degree of recovery in complex language function in order to minimise the long-lasting neurolinguistic impairment associated with very preterm birth.

**Outstanding questions and potential ways of answering them**

Despite over two decades of research on the uniqueness of language brain organisation, some questions of outstanding importance remain unanswered. Language is learnt by most humans with no effort during typical development; but what is the neural architectural blueprint that allows this unique process to take place? And how does premature environmental exposure affect it? Language is uniquely human and its brain organisation is likely to result from an evolutionary process\(^1\text{-}^4\). This functional organisation and the computational processes that distinct brain areas sub-serve are well known: but how does the underlying structural connectivity profile support distinct aspects and degrees of language computation? Is it possible that a brain area follows a distinct developmental trajectory as a result of its very early underlying pattern of structural connectivity (that is, becoming specialised for phonological rather than semantic or syntactic processing)? In this context we must also consider preterm delivery. Preterm birth results in extra-uterine exposure, which alters the developmental trajectory of neurocognitive functions at a critical, primary stage, resulting in long-lasting effects: does preterm birth affect domain-general or language-specific neurocognitive mechanisms? What brain mechanisms could be leveraged in order to at least mitigate the cognitive sequelae and shift the altered developmental curve of preterm children closer to a healthier one?

Here, we will consider some recent, cutting-edge works, tangential to the language neurobiology literature that, in the authors’ modest opinion, may propel scientists to start investigating these questions. The common framework of these approaches is to shift the focus of attention from individual white-matter tracts to brain cortical areas regarded as computational units and to consider the underlying white-matter connections as synergic parts of a computational ensemble, considering brain regions’ connectivity profile as an integrative property of their functional specialisation. Possible biological mechanisms that shape patterns of connectivity or that develop in parallel with connectivity to define function comprise molecular markers or regional properties of tissue and circuit (that is, cytoarchitecture).

Using diffusion MRI, Saygin et al. investigated whether the functional specialisation for face selectivity in the fusiform gyrus could be predicted by using only structural connectivity, as measured by diffusion-weighted imaging\(^5\). Results showed that structural connectivity between regions that have been involved in face processing (for example, the inferior and superior temporal gyrus\(^6\)) successfully predicted face-selective fusiform activation. In a more recent study, Saygin et al. extended this approach to reading by showing that word-selective visual word form area activation could be predicted by its connectivity profile expressed years earlier\(^7\). By combining machine-learning algorithms and whole-brain structural connectivity of the ventral visual stream, they were able to significantly characterise which parts of this macro-area were going to develop functional specialisation for word recognition, assessed by functional MRI three years later. Strikingly, in a period when not all five-year-old children had learnt to read, the connectivity profile of the region that would become the visual word form area was found to predispose a trajectory of computational specialisation. Although language is acquired and not learnt, it is possible that a similar approach could help us understand how neonatal brain differences in structural connectivity predict syntactic, semantic, and other complex linguistic skills that will develop in childhood, thus shedding new light on language brain ontogeny and specialisation\(^8\).

Another recent series of cutting-edge works has applied network control principles to study how the structural architecture of the human brain may constrain its own function\(^9\text{-}^4\). Structural network controllability provides a powerful mathematical framework to study a system’s (that is, the brain’s) ability...
to drive its output (that is, behaviour) towards a desired outcome through means of suitable signals (internal or external) to selected driver nodes. In a recent work, this framework was applied to study how the relatively “simple” nervous system of the Caenorhabditis elegans controls locomotion. Providing an important proof of the validity of such a framework, this study predicted and experimentally validated the involvement of individual neurons (or driver nodes) in locomotion behaviours. This type of research is of great importance as it helps characterising possible mechanistic principles that could explain why structural connectivity precedes functional specialisation. Indeed, long-distance white-matter bundles are already in place during the last trimester of gestation and may represent an architectural precursor of functional language specialisation and efficient behavioural development. Furthermore, the early characterisation of brain mechanisms underlying impaired cognitive functions in a given population may provide a mechanistic principle to foster brain plasticity through novel, targeted neurobehavioral interventions.

Conclusions
In summary, we discussed recent studies which provide an increased understanding of developmental alterations of the language network following very preterm birth. Although neurolinguistic impairments in very preterm samples are long-lasting and their severity is highly variable across individuals and partially attributable to socio-demographic characteristics, there is evidence that some adaptive mechanisms may be taking place throughout childhood. Leveraging developmental brain plasticity in language structural and functional organisation, together with stimulating rich environmental interactions, could boost adaptive processes and define compensatory pathways for complex language processing. We believe that in the immediate future the use of diffusion MRI and tractography, together with a computational framework, will shed new light on adaptive brain plasticity following preterm birth.

Competing interests
The authors declare that they have no competing interests.

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