The network properties of the brain at the time of normal birth support the acquisition of language processing

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Abstract

Language acquisition appears to rely at least in part on recruiting pre-existing brain structures. We hypothesized that the neural substrate for language can be characterized by distinct, non-trivial network properties of the brain, that modulate language acquisition early in development. We tested whether these brain network properties present at the normal age of birth predicted later language abilities, and whether these were robust against perturbation by studying infants exposed to the extreme environmental stress of preterm birth.

We found that brain network controllability and integration predicted respectively phonological, ‘bottom-up’ and syntactical, ‘top-down’ language skills at 20 months, and that syntactical but not phonological functions were modulated by premature extrauterine life. These data show that the neural substrate for language acquisition is a network property present at term corrected age. These distinct developmental trajectories may be relevant to the emergence of social interaction after birth.

1 Main text

2 Language acquisition appears to rely at least in part on the recruitment of pre-existing brain
3 structures and capacities ¹⁻³: during the last trimester of pregnancy temporal brain areas are
4 active during passive language listening ⁴⁻⁶; ventral and dorsal white-matter bundles are
5 present during early infancy ^{7,8}; and over the first months of postnatal life, infants progress
6 from a general capacity to discriminate any phonetic contrast to a more specific response to
7 the combination of vowels and consonants of their native language ⁹⁻¹¹. The establishment of
8 a phonetic repertoire allows infants progressively to infer statistical patterns in speech and
9 language structure ^{12,13} and later progress to the first production of words at 9-12 months of
10 age and multiword utterances and grammar by 18-24 months of age². Before children start to
11 read, the pre-existing connectivity profile of the visual word form area predicts its future
12 location ³, thus also suggesting that cognitive brain development also takes advantage of pre-
13 existing cortical circuits ¹⁴.

14 However, the evolution of a neural substrate for language during the perinatal period remains
15 incompletely understood. Brain development is extremely rapid at this time and normal
16 maturation is significantly disrupted by environmental pressures such as preterm birth which
17 lead to widespread abnormalities in structure and connectivity, including substantial changes
18 within regions involved in language processing ^{15,16}, which significantly predict later language
19 function. Nevertheless despite these significant abnormalities, the effect of early adversity on
20 language function is complex. Language acquisition is frequently disrupted by preterm birth.
21 However the effect is complex in preterm infants: as whilst earlier exposure to speech does
22 not alter language perception in early childhood ¹⁷, they show increasing risk of impairments
23 later in life ¹⁸⁻²¹. This suggests that some aspects of language acquisition are more susceptible
24 to environmental pressures during the preterm period than others.

From 30 to 44 weeks gestational age brain network architecture matures rapidly, and at term corrected age the brain shows scale-free macroscopic structural connectivity largely similar to the adult ^{22,23}. Although widespread abnormalities are induced by preterm birth, this is less evident on the connections between the hub nodes ²² rather than the feeder nodes of the network ^{22,24}, which therefore predicts robust network functionality is retained despite widespread damage. There is also increasing evidence that multisensory input and presumably processing across different brain systems are integral to language acquisition in the perinatal period ²⁵. This combination of factors led us to hypothesize that in preterm infants without focal destructive brain lesions, the neural substrate for language is in part a network property of the network.

Here, we examine language development in the perinatal period as properties of the large-scale structural connectivity network ²⁶, testing the prediction that network controllability and integration are critical features in effective language acquisition early in development. Studying a group of infants born preterm allowed us to investigate the effect of adverse environmental stimuli on these language network properties. We found that language abilities in early childhood are predicted by network metrics at the normal time of birth. We show that ‘bottom-up’ phonological processing is unaffected by preterm delivery while ‘top-down’ syntactic processing is altered by premature extra-uterine exposure. These results show that the neural substrate for language is at least in part a network property present at term corrected age and suggest a mechanism whereby language acquisition may support the development of social behaviors.

Results

We acquired high b value, high angular resolution diffusion weighted-magnetic resonance imaging (DW-MRI) from 43 preterm born infants (median gestational age (GA) at birth of 30 weeks) at term equivalent age (median postmenstrual age (PMA) at scan of 42 weeks) (Table S1). At 20 months of age, we formally assessed their level of cognitive and linguistic abilities. The whole-brain white-matter connectome was reconstructed using anatomically constrained probabilistic tractography²⁷, based on a 90-region parcellation from the Infant Brain Atlas for Neonates²⁸ (see *Materials and Methods*) (Fig. 1).

We used commonly used network metrics²⁶ and cross-validated multivariate models to identify the relationship between the computational properties of connections within the neonatal brain with linguistic and cognitive abilities in later childhood. We present significant results for those brain-language models after Bonferroni correction for multiple comparison. A comprehensive quantitative comparison with alternative models and random brain networks is reported in the *Supplementary information (SI)*.

Neonatal brain network controllability predicts phonologic language abilities in childhood. Diffusion MR imaging provides a rich and reproducible mapping of the macroscopic white matter connectivity network in the brain. However this mapping is not itself sufficient to understand the role of the network in neurological functions, for which further analysis of the network properties are needed²⁹. To understand whether language emerges from pre-existing connectivity patterns, we therefore asked if inter-subject differences in the perinatal structural brain network properties relate to the development of language skills in childhood?

To study the relationship between the neonatal brain's structural connectome and how its topology facilitates transition from one activity state to another, we analyzed network

controllability^{30–32}. Given constraints imposed by the brain’s underlying structural connections, this approach allowed the identification of network “controller” or “driver” sets, comprising network nodes (in this case specific brain regions) which are critical to guide the system to the activity states required for the acquisition of later language abilities. This then allowed testing of the hypothesis that synergic activity in sets of separate brain regions³³ can explain differences in language behavior.

We derived a simplified linear model from the underlying structural brain network^{34,35} (*see Materials and Methods*) and quantified structural *modal* controllability (here referred to as structural controllability) for each brain region, predicting the ability of a node to guide the system’s entire dynamics^{36,37}. Consistent with previous work which suggests that driver nodes are usually not high-degree “hub” regions, we found that structural controllability was inversely related to weighted degree (or nodal strength, the sum of the weights of the edges; Pearson’s $\rho = -0.94$) (**Fig. S1**)³². We also found that subcortical structures and the orbitofrontal cortex have the highest structural controllability scores.

To identify sets of controllers linked with the development of language skills we applied cross-validated partial least-squares (PLS) regression^{38,39} to identify linear combinations of the independent variables (in this case: brain network metrics) that maximally predict linear combinations of the dependent variables (in this case: behavioral language measures).

Having regressed out the effect of possible confounding clinical and sociodemographic factors from both the imaging data (PMA at scan; degree of prematurity (GA at birth); and sex) and behavioral measures (socioeconomic score (SES), GA at birth and sex) we found significant modes of covariation between patterns of nodal controllability at the neonatal time-point with measures of language and cognitive abilities at 2 years of age. We found that inter-individual differences in structural controllability were significantly associated with

inter-individual differences in a latent factor of language abilities, (Adjusted- $R^2 = 0.64$; p-value = 5×10^{-4} ; Mean Squared Error (MSE) = 1.9282; p-value = 5×10^{-4} ; predicted- $R^2 = 0.27$; p-value = 1.6×10^{-3} ; Mean Squared Predicted Error (MSPE) = 5.5528; p-value = 1.6×10^{-3} ; all significance values were compared against 10,000 permutations) (Fig. 2, Table 1, 2, Fig. S2). This relationship shows that subjects who exhibited higher structural control in the left superior and middle-temporal cortex were those who later exhibited greater vocabulary scores and more advanced words combination capacities. This combination of particular language abilities and brain regions, suggest that this latent factor may rely predominately on phonological skills or more general bottom-up processing of auditory-verbal material⁴⁰. This finding suggests that in the neonatal brain the left temporal and supramarginal cortices represent a network controller set which support the dynamic control of the functional brain activity which underlies later language development.

Neonatal brain network integration predicts top-down language abilities in childhood.

We then studied network brain integration to assess how the connectivity profile of an individual brain region can facilitate communication between groups of densely interconnected nodes (modules) across the brain. This is thought to represent the ability of a single brain area to rapidly combine specialized information from distributed regions⁴¹ and may represent a mechanistic property through which the brain creates complex, high-order, adaptive behavior^{42,43}.

In adults, brain cognitive systems are hierarchically distinct based on their level of network integration²⁶. Here, we calculated network integration as the *participation coefficient* (see *Materials and Methods*), measuring the diversity of inter-modular connections of individual nodes^{41,42,44} (Fig. S1). Regions with greater values of participation coefficient (close to one) have connections uniformly distributed among all of the modules, whilst regions with smaller

values (towards zero) have all of their connections within their own module. We hypothesized that network integration is an important property for neurocognitive development, and asked how network integration in the neonatal brain represents an early neural basis for the development of language skills in early childhood.

In the neonatal brain, we found that the network drivers of activity are not necessarily also brain network connector systems, as we found that network integration was not related to structural controllability (Pearson's $r = -0.01$).

By applying the same cross-validated PLS regression approach described above, we found that higher language performance in childhood was predicted by greater network integration in the left inferior, medio-prefrontal cortex, the temporal poles and right occipital gyrus (Adjusted- $R^2 = 0.75$; p -value = 1.3×10^{-3} ; MSE = 1.2543; p -value = 1.3×10^{-3} ; predicted- $R^2 = 0.26$; p -value = 2.1×10^{-3} ; MSPE = 5.5888; p -value = 2.1×10^{-3}) (Fig. 3, Table 1,2, Fig. S3). Subjects who exhibited higher network integration in the left prefrontal cortex were those that later demonstrated greater understanding of pronouns and sentences in the past tense; and later showed greater naming abilities and greater production of present progressive form or multiple-word questions. These results suggest that the prefrontal cortex acts as a network connector system which is essential for the development of later syntax and semantic language skills^{1,2,11}, in accordance with adult studies which have found that greater integration across specific networks are related to higher cognitive performance⁴⁵.

Impact of early environmental exposure on brain mechanisms of language acquisition.

To answer the question of whether *early extra-uterine exposure* affects the identified neonatal brain network mechanisms for language acquisition, we tested whether the *degree of prematurity* modulates the proposed models of language brain controllability and language brain integration. We estimated brain-behavior PLS regression models without co-varying for

the effect of GA at birth, and then split the sample into two groups of preterm infants with low and high GA at birth (Fig. S4). We then tested two separate classifiers based on the PLS individual subject weights which represent the relationship between the brain and the behavior measures (*see Materials and Methods*) and tested the effect on network controllability and integration measures separately. Using cross-validated linear discriminant analysis (LDA) we found that *only* when using the PLS subject weights derived from language brain integration could the separation between preterm infants with low and high GA be significantly predicted (respectively: language brain integration, accuracy = 0.74; p-value = 4.6×10^{-3} ; language brain controllability, accuracy = 0.58; p-value = 0.33; significance of classification was assessed against 10,000 permutations of individual subject weights) (Table 3).

We then explored how language brain integration was different between infants with low and high GA at birth by estimating a PLS model relating network integration and behavior measures separately for each group. Using a T-test, we assessed group-differences in the *PLS coefficients* that relate the original sets of brain and behavior variables to the identified PLS latent components (formally the PLS weights W^* ; *see Materials and Methods*). We found that the only significant differences were in the right superior frontal gyrus and in the right rolandic operculum (Family-wise error (FWE) corrected p-value, respectively = 2.5×10^{-2} and 3.6×10^{-2}). This result shows that preterm infants with low GA at birth have greater language network integration in the right hemisphere, suggesting those delivered earlier have a more bilateral pattern of language brain architecture at term equivalent age.

We further tested whether the modulation of degree of prematurity in the model of language brain integration could be simply explained by the correlation between GA at birth and the *brain measures* (regardless of behavior). Using a *univariate* general linear model (GLM), we

found that there was not a significant relationship between GA at birth and the regional measures of network integration (either one-tail or two-tails T-test; FWE-corrected p-values > 0.7005 , tested against 10,000 permutations). We also found that *behavioral measures* could not explain the modulation language brain integration by GA at birth (univariate GLM testing; FWE-corrected p-values > 0.1730). Finally, we also tested whether *multivariate* patterns of brain or behavior measures could significantly discriminate between preterm infants with low and high GA at birth. Using the LDA, we also found no evidence for this relationship (brain measures: accuracy = 0.58; p-value = 0.30; behavioral measures: accuracy = 0.56; p-value = 0.40; significance of classification was assessed against 10,000 permutations brain or behavior measures).

These additional analyses suggest that the modulation of language brain integration by the degree of prematurity is not due to the effect of premature birth on a single brain region or cognitive skill. Instead, premature birth appears to affect the complex brain network which underlies higher-order language abilities.

Discussion

These results demonstrate that distinct childhood language abilities can be predicted by specific network metrics in the perinatal period. This suggests that the brain's structural network is intrinsically organized to predispose itself for language acquisition. We further found that premature environmental exposure significantly affected the relationship between network features and syntactic but not phonological abilities, suggesting distinct neurodevelopment trajectories for top-down and bottom-up human language acquisition.

A structural brain network underpins efficient language learning. We show that even at the time of normal human birth, the brain's structural network already possesses specific patterns of controllability and integration within regions known to play a fundamental role in language function throughout the lifespan.

We first studied structural network controllability which predicts the ability of individual nodes (or *drivers*) to theoretically steer the network's activity output. We found that the left temporal and supramarginal cortices were key drivers of activity across the network which predict inter-subject differences in childhood language skills. In keeping with this finding, the temporal regions have been shown to be activated in an adult-like fashion during passive listening of phoneme deviants and human speech even before and around the time of normal birth^{5,6}. Here, we additionally show that language brain network controllability represents an early form of structural specialization which supports the bottom-up, phonological learning of auditory-verbal material, and may represent an early substrate for auditory-verbal working memory⁴⁰.

We then studied network integration, to measure the ability of individual nodes (or *hubs*) to facilitate global intermodular connectivity. In this context, we found that the left prefrontal cortex, the temporal poles, and the right occipital cortex, are key parts of a brain hub system

responsible for the development of receptive and expressive linguistic skills and problem solving. Previous studies have shown that the left prefrontal region responds to speech presentation by three months of age⁴, and that some degree of lateralization in response to phoneme deviance is already present in this area in the preterm brain even before term equivalent age⁶. Although it was previously thought that the left inferior frontal gyrus does not show selectivity for syntax until 9-10 years of age^{1,46}, our findings provide evidence that structural connectivity for top-down, syntactic and semantic abilities is established as a network property as early as at the normal time of birth, preceding the emergence of functional specialization and its behavioral correlate. It is also possible that these network properties may aid the learning of reading skills, through mediating the neuroarchitectural integration of the vision and language processing areas¹⁴.

Together, these findings demonstrate the presence of a structural brain network that is already organized to support environmental interaction and language learning. Of particular significance, these results are in agreement with brain network models of mature language processing and development. The left inferior and middle-frontal regions, and the superior and middle-temporal cortices are known to alter their activity during auditory-verbal working memory tasks⁴⁷ and are hypothesized to represent the brain basis underlying the learning of new words and unfamiliar phoneme combinations⁴⁰. This left language network is also thought to support core syntactic language processing in sentence-level argument structure^{48,49}. The left inferior frontal gyrus has also been postulated to specifically modulate top-down processing of sentence-level syntax^{50,51} by regulating the conversion of lexical and phonological information received from the superior temporal cortex via the arcuate fasciculus into an articulation code^{48,52,53}.

Structural controllability in this context may reflect a network property that is complementary to network integration. It is possible that direct long-distance connections already present at this age⁸ enable higher-order prefrontal areas to perform top-down modulation on structural controllers such as the temporal regions, in order to ensure efficient language learning. The presence of these two network properties at the time of normal birth may represent a required computational pathway before specific refinement through experience dependent plasticity during critical windows for language acquisition in early childhood⁵⁴.

Premature environmental exposure alters brain networks that are key for syntactic language acquisition. Although the posterior temporal areas have already started to develop the neural organization that underlies language processing before term equivalent age⁶, earlier exposure to speech in preterm infants does not lead to accelerated development of phonological skills¹⁷. Our results expand on this further by confirming that the neonatal brain network features which predict bottom-up language abilities in later childhood are minimally influenced by early environmental exposure. In contrast, we found that the prefrontal brain network architecture which predicts childhood top-down language skills such as semantic and syntactic language learning are significantly altered by premature environmental exposure. This may be because such processes are computationally more expensive than phonology and rely on connections that are not as well developed in the perinatal period as those of the temporal cortices. These findings are consistent with those of our previous study which showed that preterm birth affects the structural connectivity of sparsely-connected areas, whilst minimally impacting those related to hub regions²².

Preterm-born children are known to have difficulties in complex language attainment and function which increase with age^{55,56}. These may result from general cognitive difficulties rather than a specific phonological impairment^{20,57}, as higher-order semantic and syntactic

knowledge is thought to involve hierarchical integration across language areas and a significant working memory component¹. The results of this study show that premature environmental exposure alters the prefrontal neonatal brain network structure underlying future, top-down language learning.

Although structural network controllability represents an important step towards a novel mechanistic understanding of the human brain's structure-function relationship^{26,29}, it is nevertheless important to acknowledge the limitations of this framework^{36,37}. Although system brain dynamics may be non-linear in nature to some degree, the framework we used relied on linear modelling as such methods have been successfully applied previously to predict dynamics in the adult human brain³⁵. The assumption of linear dynamics is nevertheless true when close to operating points and over short time horizons^{36,37}.

Conclusions. In this work, we provide evidence that at the normal time of birth, in addition to known local and areal mechanisms, the neural basis for language acquisition includes properties of the overall structural brain network, and that network controllability and integration respectively underlie bottom-up and top-down language skills in childhood. We further show that preterm birth leads to specific impairment these properties that affect future semantic and syntactic learning. This work provides insight into the fundamental relationship between the early establishment of human brain network architecture and complex behavior, and has implications for fostering healthy long-term outcomes and social interaction.

Materials and methods

Infants. Preterm infants were recruited as part of the Evaluation of Preterm Imaging study (Eprime), and were imaged at term equivalent age over a 3 year period (2010-2013). The study was reviewed and approved by the National Research Ethics Service, and all infants were studied following written parental consent. A cohort of 43 preterm born infants (median age at birth of 30.14 gestational (GA) weeks; range 24 - 32; 18 females) with no evidence of focal abnormality on MRI were imaged using high-angular resolution diffusion-weighted neuroimaging at 42.14 postmenstrual (PMA) weeks (range 39 - 46).

Standardized neurodevelopmental assessment at a median age of 22 months (range: 21 – 24 months; median of 20 months corrected for prematurity) was carried out by experienced pediatricians with the *Bayley III scales of infant and toddler development* (BSID-III)⁵⁸ and of the *Parent Report of Children's Abilities Revised* (PARCAR)⁵⁹. None of these behavioral scales were significantly correlated with GA at birth or PMA at time of MRI scan. As previously described in the literature, there was a significant effect of socioeconomic score⁶⁰.

The BSID-II measures the actual cognitive and linguistic abilities that the child is able to demonstrate to the examiner during the testing session. Specifically, the receptive communication subscale aims to measure receptive language development, with items covering vocabulary and semantics (i.e. picture and object series identification; understanding of inhibitory words), and morphology and syntax (i.e. object categories identification; understanding of plurals; understanding of pronouns; understanding of past tense). Whilst the expressive communication subscale aims to test expressive language development, with its items measuring semantics (i.e. the use of one-word approximations; naming action picture series), morphology, and syntax (i.e. production of present progressive form; production of prepositions; explain how an object is used; production of multiple-word

questions). The cognitive scale aims to measure i.e. attention, problem solving, reasoning, memory, object novelty, two-step actions, size discrimination, number sequences repetition, and representational play. The PARCAR measures the level of behavioral capacities reported by the parents or guardians. 34 items are summed to give a nonverbal cognitive subscale score. Whilst linguistic development is assessed with 2 subscales that are part of the MacArthur Communicative Development Index Words and Sentences ⁶¹: a 100-word vocabulary checklist and 18 items to assess grammatical competence.

Acquisition of MRI imaging data. All MRI studies were supervised by an experienced pediatrician or nurse trained in neonatal resuscitation. Pulse oximetry, temperature, and heart rate were monitored throughout the period of image acquisition; hearing protection in the form of silicone-based putty placed in the external ear (President Putty, Coltene; Whaledent) and Mini-muffs (Natus Medical Inc.) was used for each infant. Sedation (25–50 mg/kg oral chloral hydrate) was administered to 33 infants. Imaging was acquired using an eight-channel phased array head coil on a 3-Tesla Philips Achieva MRI Scanner (Best, Netherlands) located on the Neonatal Intensive Care Unit. Whole-brain diffusion-weighted MRI data were acquired in 64 non-collinear directions with b value of 2500 s/mm² and 4 images without diffusion weighting (isotropic voxel size of 2 mm; TE= 62 ms; TR= 9000 ms). High-resolution anatomical images were acquired with pulse sequence parameters: T1 weighted 3D MPRAGE: repetition time (TR) = 17 ms, echo time (TE) = 4.6 ms, flip angle 13°, slice thickness 0.8 mm, field-of-view 210 mm, matrix 256 × 256 (voxel size: 0.82 × 0.82 × 0.8 mm); and T2 weighted fast-spin echo: TR = 8670 ms, TE = 160 ms, flip angle 90°, slice thickness 2 mm with 1 mm overlap, field-of-view 220 mm, matrix 256 × 256 (effective voxel size: 0.86 × 0.86 × 1 mm).

MRI data pre-processing. Structural MRI volumes were processed in order to extract tissues segmentation ⁶². Diffusion MRI volumes were visually inspected and processed. B0

field inhomogeneities, eddy currents, and inter-volume motion were corrected and outlier slices were replaced using topup and eddy tools in FSL5^{63–65}. B1 field bias was corrected using ITK-N4⁶⁶. All rigid registrations in native subject space were estimated using FSL boundary-based registration optimized for neonatal tissue contrasts^{67–69}; and nonlinear registrations to the T2-weighted template were estimated using Advanced Normalization Tools (ANTs)⁷⁰. All transformation pairs were calculated independently and combined into a single transform in order to reduce interpolation error. This preprocessing approach was previously published⁸.

Neonatal connectome. Estimation of fiber orientation distribution was computed through constrained spherical deconvolution with maximum spherical harmonic order of 8⁷¹. Whole-brain fiber tracking was performed using *anatomically constrained* probabilistic tractography from the MRtrix3 package with 10 million streamlines^{27,72} and SIFT2 regularization⁷³. Subject-specific weighted adjacency matrices of the brain connectome were computed based on a 90-region neonatal atlas²⁸ and edge weights were defined by the number of streamlines connecting each pair of nodes³⁶.

Dynamic model of neural function. Drawing from previous work predicting nonlinear brain dynamic processes using simplified linear models^{34,35}, we employed a noise-free linear discrete-time and time-invariant network model:

$$x(t + 1) = Ax(t) + B_K u_K(t)$$

based on the underlying structural connectome, here $x: \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}^N$ describes the state of activity of brain regions over time, and $A \in \mathbb{R}^{N \times N}$ is the structural white-matter connectome reconstructed with diffusion neuroimaging tractography streamlines. The input matrix B_K identifies the control points K in the brain where $K = \{k_1, \dots, k_m\}$ and $B_K = [e_{k_1} \dots e_{k_m}]$, and

e_i denotes the i^{th} canonical vector of dimension N . The input $u_k: \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}^m$ denotes the control strategy.

Network controllability diagnostics. We studied the controllability of this dynamical system, the capacity of steering the state of the system to a specific target state by means of an external control input⁷⁴. In other words, the capacity of manipulating the dynamic trajectories of a system.

Classic results in control theory ensure that controllability of the dynamical network model previously explicated from a set of network nodes k is equivalent to the controllability Gramian W_k being invertible, where

$$W_k = \sum_{\tau=0}^{\infty} A^{\tau} B_k B_k^{\tau} A^{\tau}.$$

In accordance with³⁶, we applied this framework to choose control nodes one at a time, and thus the input matrix B in fact reduces to a one-dimensional vector.

We studied two different quantitative, regional control strategies that describe the ability to move the network into different states.

Structural average controllability. Structural *average* controllability describes the ease of transition to many states nearby on an energy landscape (low-energy state transitions)³⁶. In accordance with previous work^{30,75}, we define $\text{Trace}(W_k)$ as a measure of average controllability, encoding the energy of the network impulse response or, equivalently, the network H_2 norm. This metric quantifies a node's capacity in moving the system to many easily reachable states and equals the average input energy from a set of control nodes and over all possible neurocognitive configurations⁷⁶.

Structural modal controllability. Structural *modal* controllability assesses the capacity of a node to control each evolutionary mode of a dynamical network⁷⁷. Modal controllability is

computed from the eigenvector matrix $V = [v_{ij}]$ of the network adjacency matrix A . By extension from the Popov-Belevitch-Hautus (PBH) eigenvector test⁷⁵, if the entry v_{ij} is small, then the j^{th} mode is poorly controllable from the node i . In accordance with³⁰, we adopt

$$\phi_i = \sum_j (1 - \lambda_j^2(A)) v_{ij}^2$$

as a scaled measure of the controllability of N modes $\lambda_0(A), \dots, \lambda_{N-1}(A)$ from the brain region i , where $\lambda(A)$ are the eigenvalues of A . This metric quantifies a node's capacity to control trajectories to all dynamical states of the network⁷⁷, hence identifying nodes sets controlling dynamic transition towards hard-to-reach (high-energy state) neurocognitive configurations.

Multi-scale community detection. In order to quantify network integration and segregation, we first identified brain network modules: groups of densely interconnected network nodes, which often are the basis for specialized subunits of cognitive processing^{78,79}. Based on a group-level neonatal brain connectome (normalized average), we performed multi-scale community detection across a range of structural resolution parameter γ ^{36,80,81}. By maximizing the modularity quality function⁸² using a Louvain-like⁸³ locally greedy algorithm⁸⁴ (with 100 optimizations) for multiple values of γ , we quantitatively estimate consensus between partitions calculating partitions similarity as z-score of the Rand coefficient⁸⁵. Maximum mean partition similarity was achieved for $\gamma = 4.8$, hinting at the presence of 18 especially well-defined modules.

Network integration. Network integration or between-module connectivity, was calculated as (weighted) participation coefficient^{42,44,86}. Quantifying strength of a region's structural interactions between modules, the participation coefficient for each region was calculated as

$$y_i^w = 1 - \sum_{m \in M} \left(\frac{k_i^w(m)}{k_i^w} \right)^2$$

where M is the set of modules, and $k_i^w(m)$ is the strengths of connections between i and all nodes in module m ^{41,87}. Regions with greater values of participation coefficient (close to one) have connections uniformly distributed among all of the modules; whilst regions with smaller values (towards zero) have all of their connections within their own modules.

Network segregation. Based on the previously identified community assignments, we estimated network segregation as within-module connectivity, by calculating the module-degree Z score (or within-module strength)^{41,87} for each brain using the following equation:

$$z_i^w = \frac{k_i^w(m_i) - k_{avg}^w(m_i)}{\sigma^{k^w(m_i)}}$$

where m is the module containing node i , $k_i^w(m_i)$ is the within-module degree of i (the weighted sum of connections between i and all other nodes in m_i), and $k_{avg}^w(m_i)$ and $\sigma^{k^w(m_i)}$ are the respective mean and standard deviation of the within-module m_i weighted degree distribution^{41,87}.

Relating neonatal brain network features with linguistic abilities in childhood. We performed a single holistic, multivariate analysis using PLS regression to simultaneously co-analyze a full set of network nodes metric at the time of normal birth along with sets of later cognitive and linguistic scores. The approach identifies linear combinations of the independent variables that maximally predict linear combinations of the dependent variables^{38,88}.

Prior to the analyses, we first regressed the effect of confound variables on brain and behavior metrics; these were PMA, GA, sex for the network nodes measures; and

socioeconomic score (SES), GA, sex for behavioral measures. All predictors and responses were standardized to have zero mean and unit variance. We evaluated different models linking brain network nodes measures with linguistic and cognitive scores. Predictor variables for each model were: (I) streamlines count; (II) weighted degree (ranked; calculated as nodal strength); (III) structural (modal) controllability (ranked); (IV) structural (average) controllability (ranked); (V) network integration (calculated as weighted participation coefficient); (VI) network segregation (calculated as within-module degree z-score); and (VII) atlas-based cortical and sub-cortical volume. All models had the same number of predictor and response variables. Response variables comprised cognitive and linguistic subscales of the BSID-III⁵⁸ (problem solving; receptive language; expressive language) and PARCAR⁵⁹ (nonverbal cognition; vocabulary; combinatorial language). Linguistic abilities at this age may not be independent of the general cognitive level, and therefore it is key to consider general cognitive development when studying language learning.

The relationship between predictor and response variables was estimated for each model using PLS regression based on the SIMPLS algorithm^{89,90}, with 10-folds cross-validation and 100 Monte-Carlo repetitions. The number of PLS components or latent factors, the linear combinations of the variables in X and Y, was chosen for each model with cross-validation in order to minimize expected error. To estimate the goodness of fit for each model we quantified R^2 , and adjusted- R^2 (normalizing for sample size and number of components), Mean Squared Error (MSE), Akaike information criterion (AIC), and Bayesian information criterion (BIC), as well as cross-validated predicted R^2 and Mean Squared Predicted Error (MSPE). To assess non-parametric statistical significance of each model we performed permutation testing. Response variables were permuted 10,000 times using Permutation Analysis of Linear Models (PALM)⁹¹ and each PLS permuted model was fitted with cross-validation and Monte-Carlo repetition as specified above.

For the significant models we characterized PLS components with statistically significant correlation between PLS scores pairs (Family-wise error (FWE) < 0.05 , corrected across PLS modes). Where XS are the predictor scores (the PLS components that are linear combinations of the variables in X); and YS the response scores (the linear combinations of the responses with which the PLS components XS have maximum covariance).

For each significant PLS mode, we extracted and normalized the PLS weights (W^*), the linear combinations of the original variables that define the PLS component^{38,88}. Given the PLS weight correlation between significant PLS components, we then studied the first principal component of W^* across the significant PLS modes in order to derive a summary measure of feature importance for each brain region. The same procedure was repeated to extract the W^* from the PLS permuted models in order to calculate the non-parametric statistical significance of each brain region (corrected for FWE across brain regions)⁹¹. To aid interpretation only brain regions with significant positive W^* were considered (one-tail FWE p-value < 0.05 , corrected across regions; corresponding to $-\log_{10}(\text{p-value}) > 1.3010$, corrected across regions)⁹². PLS weights maps not corrected for multiple comparisons are also provided (Fig. S2, S3). PLS coefficients encoding the involvement of behavioral measures in the PLS modes were also extracted and ranked. To aid the interpretation of these coefficients, we also calculated the correlation between each behavioral skill and the first principal component of W^* (PLS weights of X) across the significant PLS modes⁹³, thus scaling PLS weights of Y between 0 and 1 (Fig. 2c, 3c).

In order to deliver a more exhaustive characterization of the identified significant model, we also provide further information regarding the relation between predictors (within model) and the PLS model estimation (Fig. S5, S6, S7). All statistical analyses were performed using MATLAB (R2015b, The MathWorks, Inc., Natick, MA, USA).

Testing the effect of degree of prematurity at birth on brain-behavior links. We removed the effect of all confounds from the dependent and independent variables: PMA and sex from brain metrics; SES and sex from behavior metrics. We then used the same pipeline highlighted before to estimate PLS regression models for both language brain controllability and language brain integration. We tested the effect of premature environmental exposure on the identified brain models of language acquisition by testing whether the PLS scores pairs could discriminate between high vs low GA at birth. We split the sample onto those preterm infants with GA at birth less or equal to 29 weeks (referred as “low” GA group); and those with GA at birth greater than 29 weeks (referred as “high” GA group). A post-hoc data-driven test performed using k-means clustering confirmed the cut-off of 29 GA weeks as the optimal point to divide our sample in two groups. We performed multivariate cross-subject classification based on all estimated PLS scores pairs (or PLS individual subject weights) using cross-validated linear discriminant analysis (LDA) implemented in the FSLNets toolbox for MATLAB. Statistical significance of LDA classification accuracy was calculated with 10,000 permutation of PLS scores pairs.

The effect of postnatal age (or days of ex-utero life) was not considered a variable of interest as it is a linear combination of PMA minus GA and therefore is highly correlated (Fig. S8).

Testing significance of brain-behavior models against permuted null models and against additional covariates of interest. Aware of the caveats of structural controllability and network neuroscience³³, we also assessed the statistical significance of our brain-language results using random null models. For 1,000 times, for each participant, we randomized the individual structural brain network while simultaneously preserving the degree-, weight- and strength-distributions using the function *null_model_and_sign* from the Brain Connectivity Toolbox⁴¹. We then fed these matrices to the same pipeline and quantified PLS model goodness of fitting for random networks. This allowed us to compare the “genuine” models

- 1 of language brain network controllability and integration against the respective random null
- 2 models' distributions and calculate the non-parametric random null models-based statistical
- 3 significance.
- 4

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Author contributions. P.S., S.J.C., A.D.E. and T.A. conceptualized the study. P.S., J.D.T., T.A. and S.J.C. contributed to image processing. S.F. and A.C. carried out the behavioral data acquisition. P.S., and D.V. designed and carried out the statistical analyses. P.S. wrote the manuscript, with contributions from all other authors. S.J.C., A.D.E. and T.A. have jointly supervised the work.

Competing Interests. The authors declare no competing financial interests.

Supplementary information

Supplementary results

Alternative models of language brain acquisition. We investigated distinct brain network metrics as alternative mechanisms for explaining language brain acquisition. These alternative models were assessed with the same pipeline as above. We tested the following atlas-based brain metrics: streamlines count; weighted degree (ranked; calculated as nodal strength); structural (average) controllability (ranked); network segregation (calculated as within-module degree z-score); atlas-based cortical and sub-cortical volume. We found that none of these alternative models significantly linked neonatal brain architecture and language abilities in childhood (**Table S2**). Furthermore, the two models on interest (language brain (modal) controllability and network integration), remained significant even after Bonferroni correction across models.

Quantification of PLS model significance against random null models. Aware of the limitations and caveats of structural network controllability³³, and more in general of graph theoretical measures, we also tested the identified significant models against non-parametric permutation-based null network models. For 1,000 times, for each participant, we randomized the individual structural brain network while simultaneously preserving the degree-, weight- and strength-distributions. We then fed these matrices to the same pipeline as above and quantified PLS model goodness of fitting for random networks. This allowed us to compare the “genuine” models of language brain network controllability and integration against the respective random null models’ distributions. Crucially both models resulted to significantly relate brain-behavior pairs even against random null models (**Table S3**).

Testing the effect of additional covariates of interest in the identified brain network models of language acquisition. We performed additional tests to understand whether in-

1 scanner head-motion and cortical brain volume could have driven the estimation of brain
 2 network models of language acquisition. After regressing these variables into network
 3 connectivity, we show that models' cross-validation remained significant thus demonstrating
 4 that neither in-scanner head motion or cortical and sub-cortical volume was driving the
 5 estimation of brain network models of language acquisition (Table S4).

Figure captions

Figure 1: Exploring the link between neonatal brain network properties and the

acquisition of language in childhood. 43 preterm born infants were imaged at the time of normal birth using high b value, high-angular resolution diffusion-weighted MRI. **(a)** Whole-brain streamline tractography was performed, and the **(b)** neonatal brain structural network was reconstructed to study its emerging properties. **(c)** The involvement of each network node across the network eigenvectors was characterized. This was then used to study: **(d)** *Structural controllability*, which predicts individual nodes (or *drivers*) that are theoretically able to change a network's activity state. In this example network, the node highlighted in green is a *network driver* which can change network nodes activity and steer the system to a different state. **(e)** *Network integration*, characterizes the diversity of intermodular connections, and thus identifies individual nodes (or *hubs*) that are likely to facilitate global intermodular integration. In the example network, the node highlighted in red is a *network hub* which integrates information between two distinct network modules (circled in blue and orange). We then used Partial Least Square regression to associate neonatal brain network properties **(f)** with linguistic and cognitive skills assessed at 20 months of age **(g)**. Significant models, as well as significant model weights, were then characterized in order to quantify the brain network features related to language acquisition.

Figure 2: The left superior and middle-temporal cortex is network driver underlying the development of bottom-up language processing. We found that structural

controllability in the neonatal brain predicts bottom-up language abilities in childhood. In the identified significant relationship, neonates who exhibited significantly greater structural controllability scores at the neonatal timepoint in the left superior and middle-temporal cortex (PLS weights X, (a)), were those who later developed a larger vocabulary and more advanced language combinatorial capacities (PLS weights Y, (c)). The association between the observed and fitted behavioral skills (b) was highly significant ($\text{Adjusted-R}^2 = 0.64$; $p\text{-value} = 5 \times 10^{-4}$; colors in barplot (c) are matched with behavioral skills in scatterplot (b)). All of the significant brain network regions shown in (a) are also summarized in (Table 2a). Together these results suggest the left temporal lobe acts as a network driver of the brain activity underlying the acquisition of phonological abilities.

Figure 3: The left inferior and middle-prefrontal cortex is a network hub which supports the development of top-down language processing. We found that network integration in the neonatal brain predicts top-down linguistic abilities in childhood. In this relationship, neonates who had significantly greater network integration scores at the time of normal birth in the left inferior and medio-prefrontal cortex (PLS weights X(a)), were those who developed more advanced receptive and expressive language abilities in semantics and syntax (PLS weights Y (c)). The association between the observed and fitted behavioral skills (b) was highly significant ($\text{Adjusted-}R^2 = 0.75$; $p\text{-value} = 1.3 \times 10^{-3}$; colors in barplot (c) are matched with behavioral skills in scatterplot (b)). All of the significant brain network regions shown in (a) are also summarized in (Table 2b). These results provide the first quantitative evidence that the left prefrontal cortex at the time of normal birth has organized structural connectivity which aids the later development of top-down linguistic abilities.

Supplementary figure captions

Figure S1: Structural network controllability and integration in the neonatal human

brain. We studied the computational properties of the neonatal human brain network. Here, respectively for structural network controllability **(a)** and network integration **(b)**, we are showing normalized group-average ranked values plotted on a surface visualization.

Structural network (modal) controllability theoretically predict the ability of a brain region to guide the system's dynamics. Network integration estimate the ability to rapidly combine specialized information from distributed brain regions.

Figure S2: Non-corrected PLS weights maps from language brain controllability. For illustration purposes, we also provide a surface rendered map of the PLS weights (W^*) not corrected for multiple comparisons. For multiple-comparisons corrected PLS W^* map please refer to Figure 2a.

Figure S3: Non-corrected PLS weights maps from language brain integration. We provide a surface rendered map of the PLS W^* not corrected for multiple comparisons for the model of language brain integration. For multiple-comparisons corrected PLS W^* map please refer to Figure 3a.

Figure S4: Histogram of gestational age at birth. In blue: sample with low GA at birth (lower or equal to 29 weeks). In red: sample with high GA at birth (higher than 29 weeks). This cut-off choice was confirmed by a post-hoc, data-driven k-means clustering analyses as the optimal value to divide the sample into two groups.

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2 **Figure S5: Between-subjects correlation of network metrics are diagonally dominant.**

3 Separately for language brain controllability **(a)** and language brain integration **(b)**, here we
 4 show the cross-correlation matrices of the network metrics used as PLS predictors. Notably
 5 these are diagonally dominant: each feature is more identical to itself when compared to other
 6 features. Thus indicating that these sets of predictors carry great variance.

Across-subjects
correlation of
structural controllability
nodal metrics

Across-subjects
correlation of
network integration
nodal metrics

Figure S6: Further results from PLS model estimation for language brain

controllability. (a) PLS mode number selection based on cross-validated Mean Squared Prediction Error; **(b)** percent of explained variance for the original predictors and responses; **(c)** “Manhattan” plot of PLS components corrected for FWE across components (statistical significance was set at 1.3010 corresponding to $-\log_{10}(0.05)$); **(d)** PLS X weights (W^*) for each significant PLS component. (Each color represents the PLS W^* for a specific PLS component). Given the correlation of W^* between significant PLS components, W^* were combined across PLS components through one principal component in order to extract summary PLS W^* . **(e)** “Manhattan” plot of summary PLS W^* corrected for FWE across brain areas.

Figure S7: Further results from PLS model estimation for language brain integration.

(a) PLS mode number selection based on cross-validated Mean Squared Prediction Error; (b) percent of explained variance for the original predictors and responses; (c) "Manhattan" plot of PLS components corrected for FWE across components (statistical significance was set at 1.3010 corresponding to $-\log_{10}(0.05)$); (d) PLS X weights (W^*) for each significant PLS component. (Each color represents the PLS W^* for a specific PLS component). (e) "Manhattan" plot of summary PLS W^* corrected for FWE.

Figure S8: Scatter plots of the relation between postmenstrual age at scan, gestational age at birth, and postnatal age. Postnatal age (or days of ex-utero life) was not considered a variable of interest as it is a linear combination of postmenstrual age minus gestational age and therefore highly correlated.

Table captions

Table 1: Fit and prediction results in neonatal brain models of language acquisition.

Shown are the results of Partial Least Square (PLS) fitting and prediction for language brain controllability and language brain integration. PLS regression models were based on 10-folds cross-validation with 100 Monte-Carlo repetition and 10,000 permutations of response variable. Models were assessed on the basis of: adjusted R^2 (Adj-R2); Mean Squared Error (MSE); Akaike information criterion (AIC), and Bayesian information criterion (BIC), predicted R^2 (pred-R2); cross-validated Mean Squared Predicted Error (MSPE).

	Language brain controllability		Language brain integration	
		pvalue		pvalue
R2	0.6700	0.0005	0.7860	0.0013
Adj-R2	0.6363	0.0005	0.7503	0.0013
MSE	1.9282	0.0005	1.2543	0.0013
AIC	38.7782	0.0010	37.5237	0.0010
BIC	45.8230	0.0010	48.0909	0.0010
pred-R2	0.2659	0.0016	0.2563	0.0021
MSPE	5.5528	0.0016	5.5888	0.0021

Table 2: Brain network regions significantly involved in supporting acquisition of

language processing. Summary of brain network regions with significant PLS weights

(FWE-corrected p-value < 0.05 across all brain regions), respectively for language brain

controllability **(a)** and language brain integration **(b)**. These regions are also shown in Figure

2 and 3.

(a)

Region	AAL Abbreviation	PLS weights X (W*)	FWE pvalue
Orbitofrontal cortex (medial) right	ORBmed-R	1.8667	0.0235
Amygdala left	AMYG-L	1.5744	0.0472
Inferior parietal lobule left	IPL-L	1.5816	0.0467

Supramarginal gyrus left	SMG-L	1.5711	0.0473
Superior temporal gyrus left	STG-L	1.9501	0.0194
Superior temporal gyrus right	STG-R	1.8982	0.0212
Middle temporal gyrus left	MTG-L	1.701	0.0343

(b)

Region	AAL Abbreviation	PLS weights X (W*)	FWE pvalue
Middle frontal gyrus left	MFG-L	2.5161	0.0040
Inferior frontal gyrus (triangular) left	IFGtriang-L	1.6908	0.0360
Middle occipital gyrus right	MOG-R	2.6982	0.0025
Temporal pole (middle) left	TPOmid-L	2.2326	0.0089
Temporal pole (middle) right	TPOmid-R	1.9949	0.0175

Table 3: Language brain integration discriminates between infants with high and low

gestational age at birth. To understand whether the degree of prematurity has an effect on language brain controllability and/or integration, we trained and tested PLS individual subject weights (or PLS score pairs: XS, YS) to discriminate between neonates with low vs high GA at birth. We found that language brain integration (but not language brain controllability) carries information which significantly discriminates between infants with GA at birth lower or greater than 29 weeks, suggesting an effect of degree of prematurity specifically in this brain mechanisms for language acquisition.

	XS,YS Modal controllability (not adjusted for GA)	XS,YS Network integration (not adjusted for GA)
Accuracy	0.5814	0.7442
pvalue	0.3260	0.0046

Supplementary table captions

Table S1: Infants characteristics. This group of preterm born infants has been already object of investigation in a previously published article ⁸.

Characteristic	Value
Median (range) GA at birth (weeks)	30 (24 – 33)
Median (range) birthweight (grams)	1205 (645 – 1990)
Median (range) PMA at birth (weeks)	42 (39 – 46)
Female, no (%)	18 (42%)
Chorioamnionitis, no (%)	1 (2%)
Intrauterine growth restriction, no (%)	7 (16%)
Median (range) mechanical ventilation (days)	0 (0 – 40)
Necrotizing enterocolitis requiring surgery, no (%)	1 (2%)
Mean ($\pm$ SD) parental SES	17.4293 ($\pm$ 8.0772)

Table S2: Comparison between alternative models of language brain acquisition. We report Adj-R², MSE and MPSE values for all models tested. All models were tested using PLS regression. They were all based on the same cross-validated pipeline, with Monte-Carlo repetition, and response variable permutations; based on the same set of response variables and on an equal number of predictors. Only the models of language brain controllability and integration resulted to be significant (*) (even after Bonferroni correction across models) and had lowest MPSE and Akaike information criterion values.

	Streamlines count		Weighted degree (ranked) (nodal strenght)		Structural (modal) controllability (ranked)	
				pvalue		pvalue
R2	0.2608	0.2120	0.2975	0.2320	0.6700	0.0005 *
Adj-R2	0.2428	0.2120	0.2803	0.2320	0.6363	0.0005 *
MSE	4.3319	0.2120	4.1171	0.2320	1.9282	0.0005 *
AIC	43.0676	0.2080	42.2893	0.1590	38.7782	0.0010 *
BIC	44.8288	0.2080	44.0505	0.1590	45.8230	0.0010 *
MPSE	6.3602	0.1600	6.3679	0.1700	5.5528	0.0016 *

	Structural (average) controllability (ranked)	Network integration (weighted participation coefficient)	Network segregation (within-module degree z-score)
	pvalue	pvalue	pvalue

R2	0.0255	0.6400	0.7860	0.0013 *	0.2238	0.8000
Adj-R2	0.0017	0.6400	0.7503	0.0013 *	0.2048	0.8000
MSE	5.7112	0.6400	1.2543	0.0013 *	4.5491	0.8000
AIC	46.5332	0.6230	37.5237	0.0010 *	43.7707	0.7950
BIC	48.2944	0.6230	48.0909	0.0010 *	45.5319	0.7950
MPSE	6.3863	0.4800	5.5888	0.0021 *	7.7895	0.8200

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	Cortical and sub-cortical volume	
		pvalue
R2	0.3234	0.1950
Adj-R2	0.3069	0.1950
MSE	3.9650	0.1950
AIC	43.7707	0.7950
BIC	45.5319	0.7950
MPSE	6.3572	0.1700

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Table S3: Statistical significance against random null networks. Significant models of language brain controllability and integration were also compared against random null models. For 1,000 times, for each participant, the individual structural brain network was randomized while simultaneously preserving the degree-, weight- and strength-distributions. These individual random null networks were then linked to linguistic and cognitive measures in childhood using PLS regression. Genuine language brain controllability and integration were then compared against the estimated fitting distributions of random null networks in order to calculate statistical significance.

	Structural (modal) controllability against random null models		Network integrations against random null models	
		pvalue		pvalue
R2	0.6700	0.0010	0.7860	0.0010
Adj-R2	0.6363	0.0010	0.7503	0.0010

MSE	1.9282	0.0010	1.2543	0.0010
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Table S4: Model testing against additional covariates of interest. Brain network features of structural controllability and integration were additionally regressed for *in-scanner head-motion (a)* and *cortical brain volume (b)*. Using the same cross-validated model estimation pipeline we show that prediction results remained statistically significant, thus further demonstrating the robustness of the identified models from confounds of interest.

(a)

	Structural (modal) controllability (ranked)		Network integration (weighted participation coefficient)	
		pvalue		pvalue
R2	0.6866	0.0010	0.7861	0.0010
Adj-R2	0.6536	0.0010	0.7504	0.0010
MSE	1.8367	0.0010	1.2538	0.0010
AIC	38.3759	0.0010	37.3942	0.0010
BIC	45.4207	0.0010	47.9614	0.0010
pred-R2	0.2868	0.0020	0.2772	0.0030
MPSE	5.4730	0.0020	5.5096	0.0030

(b)

	Structural (modal) controllability (ranked)		Network integration (weighted participation coefficient)	
		pvalue		pvalue
R2	0.6410	0.0070	0.7527	0.0320
Adj-R2	0.6033	0.0070	0.7114	0.0320
MSE	2.1036	0.0070	1.4496	0.0320
AIC	39.8814	0.0040	39.2055	0.0170
BIC	46.9262	0.0040	49.7727	0.0170
pred-R2	0.2427	0.0030	0.2066	0.0030
MPSE	5.6397	0.0030	5.7725	0.0030

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