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A 10-year longitudinal fMRI study of narrative comprehension in children and adolescents

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Abstract

Comprehension of spoken narratives requires coordination of multiple language skills. As such, for normal children narrative skills develop well into the school years and, during this period, are particularly vulnerable in the face of brain injury or developmental disorder. For these reasons, we sought to determine the developmental trajectory of narrative processing using longitudinal fMRI scanning. 30 healthy children between the ages of 5 and 18 enrolled at ages 5, 6, or 7, were examined annually for up to 10 years. At each fMRI session, children were presented with a set of five, 30s-long, stories containing 9, 10, or 11 sentences designed to be understood by a 5 year old child. FMRI data analysis was conducted based on a hierarchical linear model (HLM) that was modified to investigate developmental changes while accounting for missing data and controlling for factors such as age, linguistic performance and IQ. Performance testing conducted after each scan indicated well above the chance ($p < 0.002$) comprehension performance. There was a linear increase with increasing age in bilateral superior temporal cortical activation (BA 21 and 22) linked to narrative processing. Conversely, age-related decreases in cortical activation were observed in bilateral occipital regions, cingulate and cuneus, possibly reflecting changes in the default mode networks. The dynamic changes observed in this longitudinal fMRI study support

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the increasing role of bilateral BAs 21 and 22 in narrative comprehension, involving non-domain-specific integration in order to achieve final story interpretation. The presence of a continued linear development of this area throughout childhood and teenage years with no apparent plateau, indicates that full maturation of narrative processing skills has not yet occurred and that it may be delayed to early adulthood.

Keywords

longitudinal language development; narrative comprehension; language; fMRI; child; brain; development; functional MRI

INTRODUCTION

The development of narrative comprehension skills is critical for communication. Listening to stories is a daily routine for many children and already preschool children are able to create stories that contain basic plot elements. As children develop, story structure becomes more elaborate and complex, including main and subplots. Narrative skills are not just important to oral communication, but are also linked to later literacy skills, including reading comprehension and written language skills.(Silliman 1989; Griffin, Hemphill et al. 2004; Chang 2006) This is not only true for children developing language and literacy skills in a typical fashion, but also for children who have a reading disability.(Westerveld, Gillon et al. 2008 Westerveld and Gillon 2010) Furthermore, deficits in oral narrative skills are found for a wide range of developmental disorders that affect children, including attention deficit hyperactivity disorder (Lorch, Milich et al. 1998), Down Syndrome (Bird, Cleave et al. 2008), language impairment (Copmann and Griffith 1994), learning disability (Schneider, Williams et al. 1997; Wright and Newhoff 2001), and Williams syndrome.(Marini, Martelli et al. 2010) Likewise, children with acquired disabilities, including traumatic and focal brain injury also show deficits involving narrative skills.(Kennedy and Nawrocki 2003; Chapman, Sparks et al. 2004)

The ability to comprehend a story involves coordination of a number of basic linguistic skills including phonological, semantic, and syntactic processing along with the ability to accumulate information over time and draw links between separate propositions. Narrative competence clearly rests on a base of strong linguistic skills. However it is also the case that more general cognitive skills, like verbal working memory (Karasinski and Weismer 2010) and processing capacity and speed (Montgomery, Poluenko et al. 2009) predict narrative skills. Further, children who produce complex and high quality narratives tend to have strong general cognitive skills.(Curenton 2011) Thus, both the cognitive and linguistic capacity of the child influences performance on narrative tasks.(Montgomery, Poluenko et al. 2009; Karasinski and Weismer 2010; Curenton 2011)

Given the complexity of narrative processing, and the range of skills that contribute to its development, it should not be surprising that the development of narrative skills has a protracted trajectory. Differences in narrative comprehension with age are readily detected in the early school years with increases in the number of story elements that are recalled and an increased ability to draw inferences (Vieiro and Garcia-Madruga 1997) as well as an improved ability to make connections between story elements.(Brown, Lile et al. 2011) Even in the middle school years children appear to still be acquiring narrative comprehension skills relative to that of adults.(Bohn-Gettler, Rapp et al. 2011)

Given the importance of narrative development for normal children, and its wide-spread presence in the face of pediatric disorders, understanding of the neural mechanisms

supporting this skill as it develops could be of considerable benefit from a range of perspectives. Previous imaging work has established that narrative comprehension is supported by a bilateral (left more than right) network that includes frontal, temporal and cingulate areas. These areas are involved not only in working memory and theory-of-mind processes but also in comprehension and production of language and causal-temporal ordering of information. (Long and Baynes 2002; Mar 2004; Schmithorst, Holland et al. 2006; Holland, Vannest et al. 2007; Karunanayaka, Holland et al. 2007; Kobayashi, Glover et al. 2007) Although narrative comprehension overall appears to be represented fairly symmetrically in both hemispheres, the participation of the non-dominant for language hemisphere may be increasing in response to the complexity of the contextual information. (Xu, Kemeny et al. 2005) In contrast to bilateral cortical involvement in narrative comprehension, the left perisylvian areas are typically engaged in language production and are more involved in linguistic processes that become progressively more left-lateralized with age. (Schmithorst, Holland et al. 2006; Szaflarski, Holland et al. 2006; Szaflarski, Rajagopal et al. 2012) Further, there may be some degree of change in lateralization of narrative comprehension as the participants continue processing the story with left-hemispheric language areas involved more at the onset of the story (linguistic component) and right-hemispheric language areas showing more activation at the outset of the story. This is postulated to be related to representation and synthesis of the heard sentences into a coherent whole. (Xu, Kemeny et al. 2005) The notion of bilateral cortical involvement in narrative processing is in agreement with previous studies suggestive of the presence of right hemisphere dominant network for higher order language processing (Meyer, Friederici et al. 2000) and increased right hemispheric involvement with improved semantic processing. (Donnelly, Allendorfer et al. 2011)

A recent cross-sectional study of narrative comprehension in children ages 5–18 revealed multiple neural components and functionally connected regions that participate in the narrative comprehension. (Schmithorst, Holland et al. 2006) These authors described several stepwise processes and the participation of various anatomical and functional brain areas. The first step in narrative comprehension was bilateral acoustic processing mediated via superior temporal gyri followed by semantic processing in bilateral superior temporal gyri (Friederici, Ruschemeyer et al. 2003). A left-lateralized fronto-temporal language network is recruited, either related to covert speech generation, (Schmithorst, Holland et al. 2006; Szaflarski, Schmithorst et al. 2006; Szaflarski, Holland et al. 2006) syntactic processing at the sentence level, or semantic decision and subvocal rehearsal. (Bullmore, Horwitz et al. 2000) Next, the information is reprocessed in the bilateral superior temporal gyri (non-domain-specific integrative process) with the final higher-order semantic processing occurring in the bilateral angular gyri. (Schmithorst, Holland et al. 2006) This model provides a snapshot of the anatomical and functional components of narrative comprehension but it has not fully addressed the developmental aspect of narrative processing by children and adolescents. Although the available cross-sectional data (Schmithorst, Holland et al. 2006) can suggest what the developmental trajectory might be, the *gold standard* for establishing developmental patterns is longitudinal data. Therefore, by using a within-participant methodology and longitudinal fMRI study design, we sought to characterize the dynamic changes that occur during the maturation of the brain modules involved in the narrative comprehension (rather than narrative production) in children between the ages of 5 and 18 years. The hypothesis guiding this work, based on the available literature, was that there would be bilateral increase in the involvement of the predominantly temporal regions in narrative comprehension as the children mature related to improved access to the individual words, retrieval of their meaning, and integration of information from semantic storage to discourse production. (Long and Baynes 2002; Ahmad, Balsamo et al. 2003; Kuperberg, Lakshmanan et al. 2006) This is in contrast to single word and narrative production that has been shown to involve predominantly left frontal and

temporo-parietal regions.(Long and Baynes 2002; Gaillard, Balsamo et al. 2003; Troiani, Fernandez-Seara et al. 2008; Karunanayaka, Schmithorst et al. 2010)

MATERIALS AND METHODS

Participants

In 2000, from a larger cohort of children enrolled in a cross-sectional study of normal language development (RO1 HD38578), we recruited 30 participants ages 5–7 (16 female) to take part in a longitudinal component of the study. A detailed description of the longitudinal cohort, scanning and data analysis methods is provided elsewhere.(Szaflarski, Schmithorst et al. 2006; Karunanayaka, Schmithorst et al. 2011; Szaflarski, Rajagopal et al. 2012) Here, we provide a brief description of the methods focusing on the unique aspects of the longitudinal analysis of narrative comprehension. The enrolled children were followed annually (fMRI) or biannually (neurocognitive data collection) for up to 10 years. Some children were scanned less than 10 times due to later enrollment, braces or other metallic artifacts or due to moving to another part of the country/not being available for scanning anymore (Table 1). All participants were native English speakers and had normal neurological examination prior to study enrollment. As part of the IRB-approved exclusion criteria any children with abnormal neurological examination or history of neurological problems (e.g., migraine headaches or head trauma) were excluded. All informed consent procedures were approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center in adherence to the Declaration of Helsinki.

Behavioral Testing

All children received a battery of norm-referenced tests including *Oral and Written Language Scales* (OWLS) at the time of the first scan and then in years 3 and 5 of the study and *Wechsler Intelligence Scale for Children – III* (WISC-III) at the time of the first fMRI study visit (Carrow-Woolfolk 1996). In year 6, the neurocognitive battery and post-scan questionnaire were expanded to allow detailed assessments of neurocognitive development during the second five-year period of the longitudinal study. Test results from years 6–10 are not reported here. WISC-III and OWLS scores and task performance are expected to be relatively stable during development. Consequently, average values of the scores from the first 5 years and average post-scan test scores were calculated as representative values for each participant. These measures were then included as covariates for fMRI activation in the third level of the statistical analysis model described below in Equation 1.

Functional MRI Paradigm

In this block-design fMRI task, 30 second long stories read by an adult female speaker were separated by 30 second long control conditions (see Table 2 in (Schmithorst, Holland et al. 2006) for a complete transcript of one of the stories and corresponding questions). Each story contained 9–11 sentences of contrasting syntactic constructions, inclusion of which was designed to increase the relative processing load for this aspect of language. None of the stories contained elements of the theory of mind (Kobayashi, Glover et al. 2007; Binder, Gross et al. 2011). The control condition was designed to control for sublexical auditory processing – participant heard pure tones of variable and randomly selected frequency (150, 200, 250, 500, 700, 900, or 1000 Hz) of 1 second duration at unequal intervals of 1–3 seconds. This control condition was not designed to control for phonological or word level processing and the methods used for group analysis do not explore the differences in activation for different sentence types. Participants were instructed to listen to the stories so that they could answer two multiple choice questions per story after the scans.

FMRI Data Acquisition

In years 1–8 of the study all participants underwent MRI/fMRI procedure in a 3T Bruker 30/60 scanner with the following echo-planar imaging (EPI) parameters: TR/TE 3000/38 ms, bandwidth 125 kHz, matrix 64×64, FOV 256×256 mm, slice thickness 5 mm, 24 slices acquired covering the whole brain. This was a head only human scanner equipped with a quadrature Transmit/Receive (T/R) head coil. One hundred and ten time frames were acquired, for a total scanning time of 5'30"; the first 10 frames (control condition) were discarded to allow the spins to reach relaxation equilibrium. We also collected a multi-echo reference scan in order to correct for geometric distortion and Nyquist ghosts (Schmithorst, Dardzinski et al. 2001) and a high-resolution T1-weighted 3D anatomical scan using a modified driven equilibrium Fourier transform (MDEFT) protocol: TR 15ms, TI 1100ms, TE 4.3 ms, FOV 256×192×162mm, flip angle = 20° (Duewell, Wolff et al. 1996; Wansapura, Holland et al. 1999). Twenty four fMRI scan planes were extracted from the 3D anatomical data set by interpolation for use as an anatomical underlay for activation maps.

In years 9 and 10 of the study, MRI/fMRI was performed on a 3T Phillips Achieva MRI system using dual Quasar gradients. This system replaced the Bruker 3T scanner in the same location in 2009 and was configured to be as close in function as possible to the previous system for the purposes of this longitudinal study. A quadrature T/R RF head coil was used for imaging during these years of the study. A gradient echo EPI (echo planar image) sequence was used to obtain whole brain T2*-weighted fMRI scans with parameters tuned as closely as possible to those used in the earlier years of the study on the Bruker scanner: TR/TE= 3000/38 ms, bandwidth = 267 kHz, matrix = 64 × 64, FOV = 256 × 256 mm, slice thickness = 5 mm, 35 axial slices; NR=110. Also, a T1-weighted 3D whole brain scan was acquired in the sagittal plane with the following parameters: TR/TE = 7.8/3.7 ms, FOV 240 × 240 × 164 mm, matrix 240 × 240, flip angle 8°, slice thickness = 1 mm isotropic. The same MRI compatible A/V system from Avotec, Inc. was used on both scanners. As described later, the scanner used each year is included in the statistical analysis model as a covariate of no interest.

FMRI Data Analysis

As previously, the initial fMRI image post-processing was performed using program developed in the IDL software environment (IDL 7.1; Research Systems Inc., Boulder, CO, USA).(e.g., (Karunanayaka, Kim et al. 2011; Kim, Karunanayaka et al. 2011)) Geometric distortion due to B0 field inhomogeneity was corrected during reconstruction using a multi-echo reference scan.(Schmithorst, Dardzinski et al. 2001) Data were co-registered and motion corrected using a pyramid iterative algorithm (Thevenaz, Ruttimann et al. 1998) and transformed into Talairach reference frame prior to statistical analyses.(Talairach and Tournoux 1988) Next, individual data were analyzed using a general linear model (GLM). (Friston, Holmes et al. 1995; Szaflarski, Holland et al. 2008) Individual maps were concatenated as input for the subsequent second level random effects analysis. The resulting composite maps were corrected for multiple comparisons via a Monte-Carlo simulation. (Forman, Cohen et al. 1995)

Next, for each participant at each time point the fMRI data were realigned, normalized to the Montreal Neurological Institute (MNI) template supplied with SPM8 (Wellcome Department of Cognitive Neurology, University College London, UK), and smoothed with an 8 mm Gaussian Kernel. Given that the participants range in age from 5 to 17 years of age during the 10 year course of the longitudinal imaging study, it is not possible to select an age-specific pediatric brain template that optimally accommodates normalization of all brain image data to a single reference frame. Thus, in this case we elected to use the MNI 152 template. We have previously shown that transformation of pediatric brain imaging data to

the MNI templates for adult brain is valid (Wilke, Schmithorst et al. 2002) and that differences between pediatric and adult anatomical data are relatively minor and likely negligible relative to the resolution of the fMRI data beyond the age of five. Therefore, we expect the use of the MNI framework to introduce only minor errors in co-registration across the examined age span.

All preprocessing steps including the generation of the six motion parameters (three translations and three rotations) during the realignment step were completed using SPM8. Statistical postprocessing of the longitudinal data from multiple participants scanned at multiple time points was performed using a Hierarchical Linear Model framework with mixed effect modeling. (Beckmann, Jenkinson et al. 2003) Our initial approach was to combine all original data in order to estimate the group level parameters directly from individual level time series data from each scanning visit. This was based on the fact that our data is multi-stage in that individual time series is nested within session (visit) and each session is nested within participant. This three-level model can be summarized as:

$$\begin{aligned} Y &= X_0\beta_0 + X^1\beta_1 + \varepsilon_1 \\ \beta_1 &= X^2\beta_2 + \varepsilon_2 \\ \beta_2 &= X^3\beta_3 + \varepsilon_3 \end{aligned} \quad (1)$$

where Y is the signal intensity, X^1 , X^2 and X^3 represent the first (task), second (age, scanner type) and third (IQ, OWLS, Narrative Task Performance) level design matrices containing variables of interest, and X_0 represents motion parameters. ε_1 , ε_2 , and ε_3 represent the error terms associated with the first, second and third levels of the model. However, the simultaneous estimation of the many parameters including the large number of random effects in this model makes the computation prohibitively long, on the order of ten minutes per voxel, despite using parallel computing and a large number of CPU's. To overcome this problem, we fit our data into two steps. In the first step, the time series data were fitted using a model that accounted for the serial autocorrelation that is inherent by fitting an autoregressive model AR(1). This model was fitted using an autoregressive model in SAS (SAS Institute Inc., Cary, NC) using the procedure PROC AUTOREG to estimate the parameter of interest which is the coefficient and standard error of the task variable from which we generated the contrast statistic that was used as an input into the second step of the analysis that utilized a two-stage hierarchical model. The model used in the first step of the analysis is described by the following formula:

$$\begin{aligned} Y &= \beta_0 + \beta_1 \text{task} + \beta_m \text{motion} + \varepsilon_1, \\ \text{where } \varepsilon_1 &= \rho \varepsilon_{t-1} + \varepsilon_t \end{aligned} \quad (2)$$

and where Y is the signal intensity, β_0 , β_1 and β_m ($m = 1$ to 6) are the coefficients for the intercept, task and six parameter motion respectively, ρ is the AR(1) parameter and ε_t is the error term with mean 0 and variance σ^2 . Following this, we run the two-stage hierarchical model using a mixed model participant-level analysis where the intercept and slope of age were allowed to vary from participant to participant. At this stage, there were missing data due to participants missing scan years for various reasons or not entering the study in the same year. The mixed model analysis utilized here accounted for this imbalance. The two-stage hierarchical model is described by the following formulas:

$$\begin{aligned} T &= \gamma_0 Z_0 + \gamma_1 Z_1 + \omega_1 \\ \gamma_1 &= \gamma_2 Z_2 + \omega_2 \end{aligned}$$

where T is the contrast derived from the coefficient of task (T-score) from the first step analysis (equation 2), Z_1 and Z_2 are the first (age, scanner effect) and second (IQ, OWLS, Narrative Task Performance) level design matrices while ω_1 and ω_2 correspond to the first and second level errors.

In addition to IQ (Full scale), we also investigated the impact of OWLS listening comprehension (LC) scores which is the measure of the understanding of spoken language (Carrow-Woolfolk 1996) on activation while accounting for age and IQ by including OWLS at the second level of the model. Average performance scores across the first five years were included as a level II covariate while scanner effect (Bruker or Philips), coded as 0 and 1, was included as a covariate in the Level I model. More specifically, fitting the model for linear effect of age after controlling for these covariates can be described as:

$$\begin{aligned} \text{Level I: } & T = \alpha_0 + \alpha_1 \text{age} + \alpha_2 \text{Scanner} + \varepsilon_1 \\ \text{Level II: } & \begin{cases} \alpha_0 = \alpha_3 + \alpha_4 \text{IQ} + \alpha_5 \text{OWLS} + \alpha_6 \text{Performance} + \varepsilon_2 \\ \alpha_1 = \alpha_7 + \varepsilon_3 \end{cases} \quad (3) \end{aligned}$$

Since the first level model (time series) has the same design matrix and the same number of frames for each participant at each visit, the two-stage model used here should produce a result equivalent to the full mixed mode (equation 1) described above. (Friston, Stephan et al. 2005) In order to correct for the multiple comparisons we adjusted the resulting p-values from this analysis using False Discovery Rate algorithm (FDR) and used a minimum threshold of 10 voxels to reach significance at a corrected $p < 0.05$.

The presented model fit will produce parameter estimates and the corresponding standard error for the main variable of interest age, as well as for the effects of IQ and OWLS. From these parameters a contrast map may be generated to show the effect of the task associated with these variables. We will also estimate the mean activation by fitting the model using the intercept as a predictor in order to generate the group level composite map.

RESULTS

Thirty children were included in the final sample (additional two children were enrolled but excluded from analyses due to an insufficient number of fMRI scans as a minimum of 3 fMRIs is required in order for the data to be included in analyses). Of the included participants, 27 were right-handed and 3 were left-handed as determined by the Edinburgh Handedness Inventory (EHI); the atypical handedness did not influence language lateralization or localization, as assessed with verb generation task, in any of the participants (Oldfield 1971; Szaflarski, Schmithorst et al. 2006). The maximum number of potentially available data points per participant was 1000 (10 scans with 100 EPI frames per scan). However, the number of visits per participant varied widely across participants (Table 1), underscoring the usefulness of a flexible data analysis technique able to account for missing data.

The average out-of-scanner correct response score to the multiple choice questionnaire performed after the fMRI scanning sessions in the first 5 years was 7.6 ± 1.6 with minimum of 6 out of 10 questions answered correctly by participants during 91 out of 104 scanning sessions which is well above the chance ($p < 0.002$). The OWLS mean language composite score was $108.6 \text{ SD} \pm 13$, range (81, 146), indicating normal language functioning while the OWLS LC, which is of importance for this study, was also within the normal range at $106.0 \text{ SD} \pm 19$, range (72, 160). (Carrow-Woolfolk 1996) The average Full-Scale IQ, as determined by WISC-III, was 118 ± 14 , range (99, 147), more than one

standard deviation higher than the norm, but within 1SD of the mean when compared to the WISC-IV norms and after taking into account the *Flynn effect* (Flynn 1984; Flynn 1987) A non-significant ($p=0.27$ Student's T-test) difference in mean Full-Scale IQ between the female (120) and male participants (115) was noted.

The activation pattern associated with the narrative processing task adjusted for multiple comparisons using FDR methodology is presented in Figure 1A. The composite activation map of the 30 participants is generated from fitting an intercept only model to the two level hierarchical models given in equation 2. The result of this group analysis (Figure 1A) is visually and qualitatively similar to the activation pattern seen in a cross-sectional sample of children ages 7–18 examined with the same task (Figures 1 and 3 in Schmithorst et al., 2006, N = 313) except that in the 2006 study, Schmithorst et al., showed only BOLD signal increases associated with this fMRI task (BOLD signal decreases were not reported). Overall, Figure 1A shows activations that are typical for this task in the left and right middle and superior temporal gyri (see Table 2 for the centroid location and the extent of the Brodmann's area involvement) as well as several areas of age-related decreases in BOLD signal in cingulate and occipital lobes.

The analysis of data obtained from fitting the two-level hierarchical model given in equation 3 where the t-score (from equation 2) is fitted against age while accounting for the effect of IQ, OWLS, performance and scanner effect identified brain regions with significant t-score changes with age – bilateral superior temporal gyri (Figure 1B) increases and occipital lobe, cingulate and cuneus decreases (or increases during the control condition when compared to the active condition). Restricting our data only to the activated voxels (based on the threshold value used to establish the effect of age in the two level hierarchical models) we calculated the mean t-value across these voxels and plotted this mean against age (Figure 2). This shows a linear relationship between age and mean t-values of BOLD increases in the left and right superior temporal gyri (Figure 2). We also investigated higher order models for the relationship between the mean t-value and age by fitting a quadratic model to these data. Except for isolated voxels, the quadratic effect was not significant suggesting that a linear fit adequately explains the age trend. Using equation 2 we further investigated the effect of IQ on the t-values (obtained from fitting the time series data using equation 1) after controlling for age, performance and scanner effect no significant correlation between IQ and t-value was observed. Similarly we did not find any significant correlation between the OWLS score and signal-value after accounting for the specified above covariates in the model.

DISCUSSION

The pattern of overall activation seen in this 10-year longitudinal study in pediatric participants (Figure 1A) is remarkably similar to that of the previously reported cross-sectional studies conducted in children and adolescents using the same fMRI task. The longitudinal analysis presented here confirms a maturation-dependent pattern of increased involvement of bilateral temporal brain regions in narrative comprehension. Regions expressing this maturation pattern include superior temporal gyri with the signal also present in adjacent BAs and gyri/sulci including gyrus temporalis medius and inferior and gyrus frontalis inferior and lobulus parietalis inferior (R>L) as well as the sulci dividing the above mentioned anatomical regions. More details about the specific functions of the individual regions activated by the narrative comprehension task are provided in our previous publications from the companion cross-sectional study (Schmithorst, Holland et al. 2006; Holland, Vannest et al. 2007; Karunanayaka, Holland et al. 2007) Three specific major findings emerge from our study: 1) Developmental increases in BOLD signal associated with narrative comprehension (Figure 1B) are mainly noted in bilateral middle and superior temporal gyri, 2) Maturation-associated longitudinal changes in BOLD signal related to

narrative comprehension (Figures 1B and 2) are gradual and limited to the same regions as typical for activation associated with this task, and noted over the duration of the study without reaching clear plateau or inflection indicating continuing and linear changes associated with age, and 3) Increases in BOLD signal associated with the control condition for narrative comprehension (Figures 1A and 1B) are localized to middle and posterior cingulate and occipital lobes. All these findings require a detailed discussion.

Patterns of task-related activation for narrative comprehension

Anatomically and functionally, narrative comprehension appears to be supported by a bilateral network that includes temporal and cingulate areas. These areas are involved not only in working memory and theory-of-mind processes but also in comprehension and production of language and causal-temporal ordering of information.(Mar 2004; Kobayashi, Glover et al. 2007; Binder, Gross et al. 2011) Our results are consistent with the previously reported activations in both, classic language cortex in the left hemisphere and its right hemispheric homologue. It is thought that left perisylvian activation reflects primarily linguistic processing.(Schmithorst, Holland et al. 2006; Szaflarski, Holland et al. 2006) The participation of the non-language dominant hemisphere has been suggested to contribute to the ongoing processing of the contextual information (Xu, Kemeny et al. 2005) and is in support of the previously postulated right hemisphere dominant network for higher order language processing.(Meyer, Friederici et al. 2000) As Figure 1 indicates, the overall pattern of activation was fairly symmetric and almost identical to the pattern reported in our previous studies.(Schmithorst, Holland et al. 2006; Karunanayaka, Holland et al. 2007) Some studies observed a change in lateralization of narrative comprehension as the participants continued processing the story.(Long and Baynes 2002; Xu, Kemeny et al. 2005) In these studies, left-hemispheric language areas were involved more at the onset of the story (linguistic component including comprehension of the propositional structure of the sentences) and right-hemispheric language areas showed more activation at the outset of the story – likely a result of synthesis and representation of the heard sentences into a coherent whole i.e., discourse comprehension. It may be that our nearly symmetric representation reflects the averaging of the early and late phases of story processing, which our method (developed prior to the publication of these studies) was not designed to dissociate. It should also be noted as a limitation that the present analysis does not make any attempt to separate activation differences according to the syntactic structure or semantic content of individual sentences presented. Variation in syntactic structure of the sentences was designed to increase the relative processing load only for this aspect of language rather than as a means of identifying syntax specific activation or maturational changes in activation. The sub-lexical control task and block design are not optimal for this type of analysis and the statistical analysis model described above does not support it conveniently.

Recent cross-sectional studies by our group utilizing this fMRI task in children ages 5–18 revealed multiple neural components and functionally connected regions participating in narrative comprehension.(Schmithorst, Holland et al. 2006; Karunanayaka, Holland et al. 2007; Lin, Meng et al. 2011) Based on the results of the independent component analyses (ICA) of 313 participants,(Schmithorst, Holland et al. 2006) we postulated that narrative comprehension involves several processes occurring in various anatomical and functional brain areas. In the present longitudinal study age-related increases in BOLD signal were noted only in 2 major regions – bilateral middle and left superior temporal areas with less pronounced involvement of the adjacent fronto-temporal cortices (Table 2). Although there are obvious differences in statistical power between these studies, the presence of age-related changes within participants over time is a strong confirmation of the dynamic nature of the neural substrates for narrative comprehension. It is clear that understanding how these

neural substrates are altered in the face of disorders occurring in childhood will require consideration of the age of the patients.

Despite the behavioral studies suggesting that narrative comprehension is dependent on both linguistic and more general cognitive abilities, (Montgomery, Poluenko et al. 2009; Karasinski and Weismer 2010; Curenton 2011) our analysis failed to find brain regions responsible for narrative comprehension that were specifically associated with either language or IQ test scores. This may be due to the fact that the sample participants were relatively high functioning in both cognitive and linguistic domains. Two of the studies that have found behavioral relations between narrative comprehension and cognitive skills included children or adolescents who had language disorders (Karasinski and Weismer 2010) or were from disadvantaged backgrounds.(Curenton 2011) It may be that our participants did not provide the range of scores in these domains needed to detect such a relationship.

Maturation-related longitudinal changes in narrative comprehension

The longitudinal changes observed here are bi-superior-temporal (Brodmann's Ares 21 and 22 and adjacent banks of the superior temporal sulci; Figure 1B, Table 2) with progressively and linearly increasing involvement of these areas observed during the developmental period included in the study, without reaching a clear plateau (Figure 2). This steady increase in bi-temporal involvement (after controlling for many potentially confounding factors, including IQ, linguistic abilities (OWLS), and task performance) suggests that this increase is likely a biological effect of the maturation process rather than extraneous factors. Failure of the trends for increasing activation in these regions to reach a plateau can be interpreted as continued maturation of this area without reaching its nadir. Continued development throughout the duration of the study is expected based on the fact that the maturational processes in the language cortices and the underlying white matter are ongoing and extend well into the third decade and possibly beyond.(Yakovlev and Lecours 1967; Szaflarski, Holland et al. 2006) Our own data from a group of children and adults performing a verb generation task suggest that the neural circuitry may not reach full maturity until the mid-twenties.(Szaflarski, Holland et al. 2006) It has been long recognized that the left fronto-temporal networks are involved in (and probably the driver of) language production and comprehension and that there is preponderance of activation in the dominant hemisphere with processing at the pre-lexical, word, sentence and story level.(e.g., (Meyer, Friederici et al. 2000; Gaillard, Pugliese et al. 2001; Szaflarski, Schmithorst et al. 2006; Holland, Vannest et al. 2007; Price 2010; Kim, Karunanayaka et al. 2011)) The present results demonstrate that this network contains regions that are relatively stable over time while others show age-related change in the context of a behavioral task that also shows a long developmental trajectory. It is important to note that the regions showing age-related changes do not encompass the full temporal region associated with task performance. Instead, a sub-region of this area, just posterior to primary auditory cortex (BA 21 & 22), is implicated. The presence of symmetric bilateral and continued age-related increases in this area may reflect the age-related changes in auditory signal processing that are present in early childhood and continue to the late-teenage years.(Tonnquist-Uhlen, Borg et al. 1995; Ceponiene, Rinne et al. 2002; Price 2010) The presence of continuous changes with age could also explain the lack of asymptote in the Figure 2. The patterns of activation associated with the narrative comprehension task together with the use of the HMLM analysis tend to restrict the possible findings of maturational changes to the bilateral temporal regions.

Clear age-associated BOLD signal increases in the left fronto-temporal language networks were also seen in our previous longitudinal study of a verb generation task.(Szaflarski, Schmithorst et al. 2006) That study showed, however, that the age-related changes included left inferior and middle frontal cortex along with left inferior and middle temporal gyri). The

parallel developmental change in homologous areas of the temporal lobes was not seen in our previous longitudinal study. However, the verb generation task used in that study is known to activate predominantly left hemispheric regions.(Petersen, Fox et al. 1988; Szaflarski, Schmithorst et al. 2006) Given that the same participants were included in both the verb generation and present narrative processing studies, it is clear that these age-related changes reflect an interaction between maturation and the nature of the language task.

The present developmental study confirmed the previous findings of various cross-sectional studies that the participation of the left fronto-temporal network in language development in early childhood years increases with increasing age, which may be one of the reasons for stronger left-lateralization of language functions observed with brain maturation in children. (Gaillard, Hertz-Pannier et al. 2000; Schlaggar, Brown et al. 2002; Szaflarski, Schmithorst et al. 2006; Szaflarski, Holland et al. 2006) Although, as expected, narrative comprehension activated somewhat different cortical modules in the left temporal lobe when compared to verb generation and other language tasks,(Szaflarski, Binder et al. 2002; Holland, Vannest et al. 2007) the results of our study provide evidence of increasing participation of the left temporal lobe in age-associated language development and expand these observation to the right-hemispheric homologue. This finding is consistent with one of the developmental modules identified in the cross-sectional study of narrative comprehension by our group (Schmithorst, Holland et al. 2006; Karunanayaka, Holland et al. 2007) and similar to a study that evaluated fable story reading in 8–13 years old children.(Gaillard, Pugliese et al. 2001) The fact that the last study did not find any age-related increases in the degree or extent in BOLD signal changes is not necessarily in disagreement with our results; that study enrolled older children (8–13 year old) and included a very small sample of only 9 individuals making detection of such findings almost impossible. In fact, participants included in the current longitudinal study may be too old to show some of the age-related changes associated with this task, as narrative comprehension starts developing at the age of 2 and shows significant complexity at the age 4, long before participants are able to routinely participate in fMRI studies.(van den Broek, Lorch et al. 1996; Alexander, Miller et al. 2001; Byars, Holland et al. 2002)

BOLD signal decreases associated with narrative comprehension

In addition to BOLD signal increases with this narrative comprehension fMRI task, several areas of BOLD signal decreases (or increases related to the control condition) were observed. In general, the deactivations observed in the GLM analysis (Figure 1A) were more extensive than in the longitudinal (maturation) portion of the analysis (Figure 1B) but a clear overlap should be noted (Table 2). These activations are not what would be expected from a sublexical auditory task that does not require attention and does not have linguistic, emotional or performance components (i.e., simple listening to trains of modulated tones was employed here). In fact, our expectation was to observe, at least in the 2nd level group analysis (Figure 1A), activations in the primary auditory cortices – Heschl's gyri bilaterally. (Morosan, Rademacher et al. 2001) Thus, the finding of symmetric deactivations and of the age-relationship in the bilateral middle occipital gyri, mid- and retro-splenial portions of the cingulate gyri raises the possibility of additional processes co-occurring in the control stage of this task.

One plausible explanation for this finding is that during the control condition the spontaneous brain activity overtakes the task-related activity.(Fox and Raichle 2007) While typically multiple cortical and subcortical areas are activated during the so-called resting state (fluctuation between intro- and extro-spection), the presence or absence of these areas on fMRI images may be modulated by fMRI task content (i.e., the active as well as the resting conditions).(Fox, Snyder et al. 2005) The theories put forward to explain these findings are that there is either reorganization of the facilitatory and inhibitory processes in

the brain or that while the brain activity remains overall constant between active and control conditions, the observed fluctuations are due to the contrast between the spontaneous and task-related activity.(Fox and Raichle 2007) Of course, the above could explain only the presence of deactivations in the mid- and posterior/retrosplenial portions of the cingulate gyrus that were previously observed in studies of resting state networks.(e.g., (Morgan, Gore et al. 2008; Kay, Meng et al. 2012)) Another plausible explanation for these deactivations is the presence/absence of alpha-rhythm correlates.(Goldman, Stern et al. 2002; Laufs, Kleinschmidt et al. 2003; DiFrancesco, Holland et al. 2008) As the alpha rhythm becomes more apparent during rest with eyes closed and the power of alpha rhythm increases with age, the deactivations observed in the cingulate and occipital head regions are in line with the findings from the above mentioned studies and can also explain the age-related BOLD signal changes (Figure 1B; Table 2).(Samson-Dollfus, Delapierre et al. 1997)

CONCLUSIONS

In summary, we have shown that both superior temporal lobes and adjacent areas participate in narrative comprehension in children and their participation increases with age between 5 and 18 years without reaching plateau or inflection. Future longitudinal studies should focus on evaluating earlier and later developmental processes and on comparing interventions in participants with abnormal development of narrative comprehension.

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Highlights

- First ever 10-year longitudinal study of narrative comprehension in children
- Novel, flexible data analysis methods accounts for intra-/inter-participant variability
- HLM used for statistical post-processing of the longitudinal fMRI data
- Linear increase of bi-temporal involvement in narrative comprehension observed
- Negative activations observed in DMN during control task

Figure 1.

Significant activations in response to the narrative processing task for all healthy children enrolled in this study. Both figures are presented in neurological convention (left on the picture corresponds to the left hemisphere). Activated voxels are superimposed on a normalized T1 weighted image generated from one of the participants with 12 axial slices selected for display (Z left upper corner slide = -26; Z right lower corner = 29). All regions are significant with $p < 0.05$ corrected for multiple voxel comparisons. **A.** GLM composite map incorporates all participants and all annual visits for which usable data points were obtained. For exact location of the BOLD signal changes see Table 2. **B.** Regions with significant longitudinal positive BOLD signal changes associated with age (minimal longitudinal negative changes were also observed) after accounting for IQ, OWLS, scanner, and performance effects. For exact location of the BOLD signal changes see Table 2.

Figure 2.

Plots of the mean t-values of activated voxels against age in years. Voxels included in the average are those that exceeded the threshold used to establish the effect of age in the two level hierarchical models in Figure 1B. Error bars represent the standard error of the mean t-value across participants. Blue (solid line) and black (dashed line) correspond to hemispheric regions of the longitudinal BOLD signal increases with age from Figure 1B.

Table 1

Breakdown of the total number of visits, number of visits where the story processing task was successfully administered (scan visits) and age at the first visit. Failure to receive all 10 fMRIs was due to factors such as late enrollment in the study, orthodontic braces being installed, or the family leaving the Greater Cincinnati area.

Participant	Total Visits	Scan Visits	Age at Entry
05F003	7	6	5
05F004	9	9	5
05F008	6	6	5
05M002	7	5	5
05M003	10	10	5
05M005	7	7	5
05M019	7	7	5
05M024	3	3	5
06F001	5	5	6
06F011	8	8	6
06F014	3	3	6
06F018	7	7	6
06M001	10	9	6
06M005	10	10	6
06M012	8	8	6
07F001	4	4	7
07F002	9	9	7
07F005	5	5	7
07F007	9	9	7
07F009	9	9	7
07F010	9	9	7
07F015	8	8	7
07F021	9	9	7
07F024	8	8	7
07M001	10	10	7
07M004	8	8	7
07M005	7	7	7
07M006	10	10	7
07M009	10	10	7
07M012	4	4	7

Table 2

Talairach Coordinates of the centroids and Brodmann's areas (BAs) for the regions displayed in Figure 1A and 1B

Location	BA	X, Y, Z
Figure 1A: Localization of BOLD signal changes		
BOLD signal increases		
L. Superior Temporal Gyrus *	20, 21, 22, 37, 44, 45	-54, -14, 2
R. Superior Temporal Gyrus *	20, 21, 22, 37, 44, 45	51, -13, 4
BOLD signal decreases		
L. Middle Occipital Gyrus	18, 19	-36, -71, 4
R. Middle Occipital Gyrus	18, 19	33, -76, 1
Cingulate gyrus (posterior)	29, 30	2, -64, 9
Cingulate gyrus (middle portion)	23	-1, -13, 25
Figure 1B: Localization of BOLD signal changes associated with age		
BOLD signal increases		
L. Superior Temporal Gyrus **	21, 22	-59, -22, -3
R Superior Temporal Gyrus **	21, 22	56, -23, 4
BOLD signal decreases		
Cingulate Gyrus	23	0, -22, 31
R Inferior Occipital Gyrus	18	31, -84, -6
L Inferior Occipital Gyrus	18	-27, -83, -4
R Cuneus	31	2, -73, 11

* left and right centroids for these BOLD signal increases are located over the superior temporal gyri / BAs 21 and 22 but the signal is also present in adjacent BAs and gyri/sulci including gyrus temporalis medius and inferior and gyrus frontalis inferior and lobulus parietalis inferior (R>L) as well as the sulci dividing the above mentioned anatomical regions;

** signal is also noted in the banks of the superior temporal sulcus; BOLD – blood oxygenation level dependent.