

The development of functional and effective connectivity for narrative processing in children investigated via functional MRI and Multivariate Autoregressive Modeling

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Introduction

During the early school years, school performance is significantly impacted by story comprehension skills [1]. To investigate the neural correlates of auditory sentence processing and narrative comprehension in children, we performed a large-scale study using fMRI involving children ages 5-18 years old. We proposed to investigate the functional connectivity involved in this task and how it develops with age. In addition, we used a recently published method, Multivariate Autoregressive Modeling (MAR) [2], and modified it for a multi-subject analysis in order to investigate effective connectivity and its development with age.

Materials and Methods

302 children (145 boys, 157 girls) were successfully scanned as part of this study. MRI scans were obtained using a Bruker 3T Medspec imaging system. EPI-fMRI scan parameters were: TR/TE = 3000/38 ms; BW = 125 kHz; FOV = 25.6 X 25.6 cm; matrix = 64 X 64; slice thickness = 5 mm. The fMRI scan paradigm consisted of a 30 second on-off block design. One story, read by an adult female speaker, was presented during each 30 s task period. Each story contained 9, 10, or 11 sentences of contrasting syntactic constructions (e.g. conjoined sentences vs. center embeddings). During each 30 s control period, pure tones of 1 s duration were presented at unequal intervals of 1 to 3 s. The control condition was designed to control for sublexical auditory processing.

Data was processed using in-house software written in IDL (Research Systems Inc., Boulder, CO). The General Linear Model (GLM) was used to find regions with significant functional activation (Figure 1); the threshold used was a nominal $p < 1e-10$ (Bonferroni-corrected $p < 1e-5$). To investigate functional connectivity, ROIs were drawn around each of the regions (left Wernicke's area; right Wernicke's area; left Broca's area; middle frontal gyrus). For each subject, the correlation coefficients were computed between each pair of regions and converted to Z-scores using Fisher's Z transformation. The Z-scores were tested both for overall significance using a one-sample T-test, as well as for significant correlations with age. To investigate effective connectivity, the MAR technique was used with a model order of 2. In the MAR approach [2], each point in each fMRI time course is modeled as a linear combination of preceding time points from all regions, thus yielding information about effective connectivity without the need for an *a priori* model, as is necessary in Structural Equation Modeling (SEM). The T-scores from each MAR connection are then used in a second-level analysis to test for overall significance as well as correlations with age.

Results and Discussion

Using a one-sample T-test, significant ($p < 0.001$) overall functional connectivity was found between each pair of regions, as expected since each region was involved with the cognitive task. The pairwise connectivity between left Wernicke's and right Wernicke's areas ($R = 0.29$, $p < 0.001$), left Wernicke's and Broca's area ($R = 0.17$, $p < 0.01$), and right Wernicke's and Broca's area ($R = 0.17$, $p < 0.01$) displayed significant increases with age. For the MAR analysis, using a one-sample T-test, and a criterion of $d > 0.4$ ($T > 6.95$, $p < 0.001$) the significant path connections are diagrammed in Figure 2 for the time courses delayed by one time point. The results indicate a feedback network from Broca's area and the middle frontal gyrus to Wernicke's areas in both hemispheres. The path from Broca's area to Wernicke's area in the left hemisphere was also found to be significantly correlated with age ($R = 0.18$, $p < 0.005$).

The MAR results are in agreement with a recent evoked-potential study [3] showing bi-directional connectivity between Broca's and Wernicke's areas. This hypothesis is in line with recent "connectionist" models of language processing [4], and also with a recently proposed dynamic model for interaction between semantic and syntactic processing [5]. Our results, with a significant age-related change in effective connectivity between Broca's and Wernicke's area in the left hemisphere, support the hypothesis that this interaction develops with age, and agree with a diffusion tensor imaging (DTI) study showing age-related increases in fractional anisotropy (FA) in the arcuate fasciculus, connecting Broca's and Wernicke's areas, in children in this age range [6].

While our study involved a large number of subjects, the relatively large effect size found indicates that MAR may be a feasible way to investigate effective connectivity without an *a priori* model in fMRI studies involving smaller numbers of subjects. Data-driven linear Structural Equation Modeling (SEM) approaches are susceptible to sample-specific confounds [7]. A limitation of our study was the rather long TR used (3 seconds), which obviated the ability to search for effective connectivity over a shorter time period, a likely reason why a significant feed-forward connection from Wernicke's area to Broca's area was not seen.

Conclusion

An fMRI study involving narrative comprehension was conducted on a cohort of children ages 5-18. Functional connectivity between Broca's area and Wernicke's areas in both hemispheres was shown to increase with age. In addition, using multivariate autoregressive modeling (MAR) feedback networks were found involving effective connectivity from Broca's area and the middle frontal gyrus to Wernicke's areas, and the effective connectivity from Broca's area to Wernicke's area in the left hemisphere was shown to increase with age. The results demonstrate the feasibility of performing multi-subject MAR analyses to investigate effective connectivity in the absence of an *a priori* model.

References

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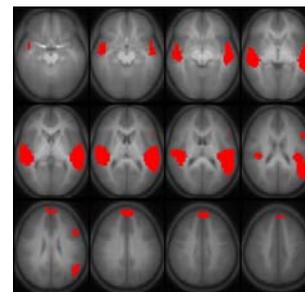


Figure 1. Regions active ($p < 1e-5$, corrected) for the task of narrative processing performed by 302 normal children.

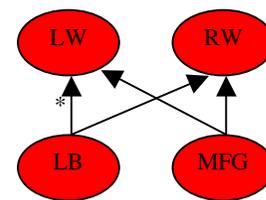


Figure 2. Feed-back networks found from multivariate autoregressive modeling (MAR) analysis. All path connections are significant with $p < 0.001$ ($d > 0.4$). (LW = left Wernicke's area; RW = right Wernicke's area; LB = left Broca's areas; MFG = middle frontal gyrus). * = significantly correlated with subject age ($R = 0.18$; $p < 0.005$).