Published in final edited form as:

Brain Lang. 2013 May ; 125(2): 156–164. doi:10.1016/j.bandl.2012.07.003.

Time-constrained functional connectivity analysis of cortical networks underlying phonological decoding in typically developing school-aged children: A magnetoencephalography study

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Abstract

The study investigated functional associations between left hemisphere occipitotemporal, temporoparietal, and inferior frontal regions during oral pseudoword reading in 58 school-aged children with typical reading skills (aged 10.4±1.6, range 7.5–12.5 years). Event-related neuromagnetic data were used to compute source-current density waveforms using a minimum norm algorithm. Temporally-constrained contributions were established for four ROIs (STG, SMG, ANG, and IFG) by controlling for the autoregressive effects of activity in each ROI. Unique contributions made by activity in one ROI to subsequent activity in a second ROI were assessed through multiple regression analyses. Forward associations between lateral (LOC) and ventral occipitotemporal cortices (fusiform gyrus) to each of the four main ROIs were also examined. The earliest significant contributions to SMG and ANG activation (at 200–250 ms) were made by preceding activity in the fusiform gyrus. The degree of activity in IFG appeared to be determined by earlier activity in ANG and STG.

Keywords

reading; cortical connections; superior temporal gyrus; inferior frontal gyrus; angular gyrus; supramarginal gyrus

Introduction

It is generally accepted that the neural correlates of phonological decoding skills critical for the successful acquisition of reading are supported by distinct cortical mechanisms in the dominant left hemisphere. In particular, graphemic processing, including integration of orthographic, phonological and morphological information derived from printed text, is

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thought to be mediated by neurophysiological processes operating in the ventral occipito-temporal cortex (mainly in the fusiform gyrus; Flowers et al., 2004; McCandliss, Cohen, & Dehaene, 2003; Pammer et al., 2004; Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005). The temporo-parietal cortex, encompassing the inferior parietal (supramarginal and angular gyri) and the posterior superior temporal region, have been shown to be indispensable to phonological processing of both spoken and printed stimuli (Beauvois & Derouesne, 1979; Binder et al., 2003; Caplan, Gow, & Makris, 1995; Joseph, Noble, & Eden, 2001; Joubert et al., 2004; Roux et al., 2004; Simos et al., 1999, 2000).

Neurophysiological processes that take place in these posterior circuits are complemented by engagement of the inferior frontal cortex, associated with activation of articulatory representations (phonological recoding; Mainy, Jung, Baciú et al., 2008; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Sandak, Mencl, Frost, & Pugh, 2004).

To a large extent, delineation of the brain circuits underlying word-level skills using hemodynamic imaging methods have relied on contrast-based statistical approaches, focusing on regions of activation and/or deactivation. However, adequate description of a given brain circuit (or network) requires identification of all key regions which are indispensable for the function in question, as well as the manner in which these areas interact. With respect to the latter, methodological developments in the analysis of functional magnetic resonance (fMRI) and positron emission tomography (PET) time-series have provided various approaches for quantifying putative neural networks, generally concurring with theoretical models emphasizing distinct posterior and anterior components. Results are also in agreement with anatomical models of structural connectivity highlighting key white matter pathways linking the network of left hemisphere regions that support reading (e.g., Lawes et al., 2008).

The representation of networks supporting word-level reading was initially demonstrated using measures of *functional connectivity*, based on the degree of covariance in the degree of activity noted in each region during the performance of tasks that exemplify the function (Bullmore et al., 2000; Mechelli, Penny, Price, Gitelman, & Friston, 2002). In particular, using PET, Horowitz Rumsey, & Donohue (1998) reported significant positive correlations between regional blood flow in the left angular gyrus and blood flow in extrastriate occipital and temporal lobe regions, in non-reading impaired male adults, during single pseudoword and exception word reading, a finding supported subsequently using fMRI (Pugh et al., 2000).

Further insight into the dynamics of neural networks underlying word-level reading has been obtained using estimates of *effective connectivity*, which model networks based on statistical inferences made regarding the directional influence of one cortical region over another (Friston, Harrison, & Penny, 2003; Mechelli, Price, Noppeney, & Friston, 2003; Penny, 2004). For example, using fMRI and dynamic causal modeling (DCM), Bitan et al. (2005) reported differential modulations in the intrinsic connectivity of left-hemisphere language regions (fusiform, inferior frontal, lateral temporal and inferior parietal cortices), with phonological (rhyming) and orthographic (spelling) judgments. Results suggested stronger convergence of neural influences to the lateral temporal and inferior parietal regions, respectively, implying that these foci are crucial for integrating task-dependent neural signals. While replicating these findings, a subsequent study by the same group also found the modulation of connectivity from inferior frontal to temporoparietal regions to be significantly weaker in children, relative to adults, suggesting that increased top-down control in adults may facilitate orthographic and phonological processing in this group (Bitan et al., 2006). Similarly, normative, developmental effects on top-down control during reading were noted by Bitan, Cheon, Burman, & Booth (2009), who reported an age-related increase in the influence of the left inferior frontal region on the lateral temporal cortex,

during word judgment tasks involving conflict of orthographic and phonological information. Interestingly, the latter study also noted a developmental increase in bottom-up processing, as characterized by increased modulatory effects from the fusiform gyrus to the lateral temporal cortex.

Furthermore, additional representations of networks underlying reading have also been reported using models of *effective connectivity*. For example, during execution of a demanding rhyming task, Booth et al. (2007) used DCM to demonstrate stronger reciprocal connections between the cerebellum and left inferior frontal and lateral temporal cortices, contrasted by weaker unidirectional connections between the latter two regions and the putamen. These findings suggested a role of the cerebellum in the development of word-level skills through its involvement in motor planning/control and in regulating the timing of language processes (see also, Ben-Yehudah & Fiez, 2008; Cooper, Grube, Von Kriegstein et al., 2012). Moreover, an fMRI study by Levy et al. (2009) utilized structural equation modeling (SEM) to quantify components of the ‘dual-route cascade’ model of reading (Coltheart, Rastle, Perry, Langdon, & Ziegler, 1993), reporting stronger connections between the left middle occipital and lateral occipito-temporal, and subsequently inferior frontal, cortices, during real word reading (ventral pathway). In comparison, the current study corroborated the dorsal pathway’s involvement in grapheme-to-phoneme conversion, demonstrating connectivity between the left middle occipital, lateral occipito-temporal, lateral parietal, and inferior frontal, cortex, during pseudoword reading.

In view of the spatial resolution afforded by PET and fMRI, it is highly likely that activation (or deactivation) maps obtained using these techniques reflect the core components of networks that underlie word-level skills. However, due to limited temporal resolution inherent in the generation and measurement of hemodynamic responses, neural networks for reading—particularly those derived using measures of effective connectivity—may be better characterized by application of alternative imaging approaches, such as magnetoencephalography (MEG). MEG indexes neuronal activation with millisecond temporal resolution necessary for real-time visualization of brain network dynamics. Recent developments in the analysis of MEG time series have demonstrated the utility of this imaging method in studying brain networks, particularly those associated with reading (Gross et al., 2001; Salmelin & Kujala, 2006). Specifically, Kujala and colleagues (2007) applied a voxel-wise coherence analysis to MEG time series (Dynamic Imaging of Coherence Sources) reporting a densely connected network of regions, obtained in the context of a rapid serial visual presentation (RSVP) paradigm, to simulate natural reading. In accord with regions implicated in previous imaging studies of reading, these authors localized long-range neural connections, dominated by feed-forward connections from the left inferior occipito-temporal cortex to the cerebellum, superior temporal, anterior inferior temporal, precentral, insular, prefrontal and orbitofrontal cortices, in the 8–13 Hz range. However, with the exception of the latter study, examples of the feasibility of MEG as a tool for studying connectivity, and more specifically, for quantifying neural networks supporting word-level skills are yet to appear in the literature.

MEG recordings during performance of word and pseudoword reading in children with typical developmental histories reveal a pattern of brain activity featuring early activation in lateral and ventral occipitotemporal regions followed by temporoparietal activity. Only after a significant temporal delay, neurophysiological activity in inferior frontal cortices, mainly in the left hemisphere, is noted (Simos et al., 2005, 2007a,b). The statistical properties of the activation data obtained in these studies, however, did not permit correlational analyses which could throw additional light into the functional interdependencies of neurophysiological activation across these key brain regions. Thus, although a tentative sequence of neurophysiological events across regions was established, it was not possible to

determine which areas were likely to contribute, through feed-forward connections, to the engagement of neurophysiological events in brain areas that showed activity at later stages of stimulus processing. Importantly, the magnetic source estimation technique employed in these studies did not allow for modeling of activity in all possible brain regions simultaneously. This type of information is crucial in addressing an important issue in connectivity studies employing hemodynamic data, namely the selection of the most appropriate structural model to test, given the enormous complexity of the full model (i.e., a model that contains all possible ROIs and paths).

Based on previous reports on the cortical areas that constitute major components of the brain mechanism for phonological decoding in children (e.g., Démonet, Taylor, & Chaix, 2004; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Maisog et al., 2008; Shaywitz, Lyon, & Shaywitz, 2006; Schlaggar & McCandliss, 2007), here we explore the timing and functional cortico-cortical associations between four key left hemisphere areas for phonological decoding: the angular (ANG), supramarginal (SMG), superior temporal (STG) and inferior frontal gyri (pars opercularis and pars triangularis; IFG). These are regions where significant differences between typical and reading impaired students are found in hemodynamic (Shaywitz et al., 2002; Cao, Bitan, Chou, Burman, & Booth, 2006; Hoeft et al., 2007a,b; Maisog et al., 2008; van der Mark et al., 2009; Temple et al., 2001; Eden & Zeffiro, 1998) and neuromagnetic studies (Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000; Simos et al., 2011). The occurrence and latency of feed-forward associations between two visual association areas (lateral [LOC] and ventral occipitotemporal region [fusiform gyrus]) and each of the aforementioned temporoparietal and inferior frontal ROIs were also assessed.

MEG recordings were obtained from 58 non-reading impaired, elementary school students in the context of a pseudoword naming task, and analyzed at the source level using a minimum norm estimation algorithm (Hämäläinen & Ilmoniemi, 1994; Dale Fischl, & Sereno, 1999). The dependent measure derived by this procedure is instantaneous electrical current in small cortical patches composing ROIs of interest, in the form of time series, covering the crucial time window between stimulus presentation and the preparation of a spoken response, at 4-ms time intervals. This type of data affords adequate temporal and spatial resolution to determine if the degree of activity in the six ROIs at a particular time window accounts for a significant portion of variance in the degree of activity in each of the four temporoparietal and inferior frontal target regions at later time windows. Temporally-constrained contributions, which may be interpreted as the result of inter-regional neuronal signaling, were established by controlling for the autoregressive effects of activity in each of the ROIs involved in the analyses. Finally, the unique contributions made by activity in one ROI to later activity in a second ROI were assessed through multiple regression analyses.

Methods

Participants

The current sample included 58 right-handed children (28 boys and 30 girls, with a mean age of 10.4 ± 1.6 , range 7.5–12.5 years) who had never experienced difficulties in reading and scored > 90 on the Basic Reading Composite (average of Word Attack and Letter-Word Identification subtest scores of the Woodcock-Johnson Tests of Achievement-III [W-J III]; Woodcock, McGrew, & Mather, 2001). The Composite group mean was 106 ± 10 points (range 90–126 points) on WJ-III Word Attack and 105 ± 11 points (range: 89–130) on WJ-III Letter-Word Identification. Corresponding values for Verbal, Performance, and Full-Scale IQ (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999) were 111 ± 16 points (range: 86–144), 104 ± 11 points (range: 83–125), and 108 ± 14 points (range: 84–130). Twenty-seven students were Caucasian, fifteen were Hispanic, and 18 African-American. Participants were selected for inclusion in the sample only if they had T scores < 55 on the

Attention and Hyperactivity CBCL scales (Child Behavior Checklist, Parental Form; Achenbach, 1991) or a mean score lower than 1.67 points on the parental ADHD-C SNAP-IV scale (Swanson, 1992) indicating low risk for ADHD (Chen, Faraone, Biederman, & Tsuang, 1994).

Procedures

Tasks—Participants were tested on an oral pseudoword reading task, involving three-letter pronounceable non-words (e.g., *lan*), subtending 2.0° of horizontal visual angle. A total of 100 stimuli were presented randomly, arranged in four blocks of 25 items each. Stimuli were presented for 1 sec, one at a time (with a randomly varied interstimulus interval of 3–4 sec), through a Sony LCD projector (Model VPL-PX21) on a back-projection screen located approximately 60 cm in front of the participant. A rather long ISI was used in order to minimize myogenic and movement artifacts associated with speech on the MEG data recorded in response to the next stimulus in the series.

Imaging procedures—Magnetic source imaging (MSI) involved, first, recording event-related magnetoencephalographic data segments with a whole-head neuromagnetometer array (4-D Neuroimaging, Magnes WH3600), that consisted of 248 first-order axial gradiometer coils, housed in a magnetically shielded chamber and arranged to cover the entire head surface. The magnetic flux measurements were digitized at 250 Hz, filtered with a bandpass filter between 0.1 and 20 Hz and subjected to a noise reduction algorithm that is part of the 4D-Neuroimaging software. The single-trial event-related field segments (ERFs) in response to 70–80 stimulus presentations, were averaged after excluding those containing eye movement or other myogenic or mechanical artifacts.

To identify the intracranial origin of ERFs the magnetic flux distribution recorded simultaneously over the entire head surface at successive points (4 ms apart) was analyzed using a minimum norm model to obtain estimates of the time-varying strength of intracranial currents (MNE Software, v. 2.5 <http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/index.php>). This method affords greater spatial resolution, as compared to the more traditional and externally validated source localization method of the single equivalent current dipole, and allows detection of simultaneous magnetic sources distributed along the entire cortical surface. The model assumes a continuous distribution of current along the cortical surface which has some minimum norm (Hämäläinen & Ilmoniemi, 1994). Estimated current sources were anatomically constrained by an MRI-derived surface model of each participant's brain. This surface model was generated by a fully-automated cortical surface reconstruction procedure using FreeSurfer software (Dale, Fischl & Sereno, 1999) for producing a detailed geometric description of the gray-white matter boundary of the neocortical mantle and the mesial temporal lobe. The program employs triangular tessellation (triangle size ~ 1 mm) to define the cortical surface as a mesh consisting of approximately 150,000 vertices (depending on each subject's cortical surface area). The source-space is subsequently reduced by downsampling for computation purposes to approximately 3,000 vertices per hemisphere (using grid spacing of 7 mm). Each vertex represents the location of a potential current dipole perpendicular to the cortical surface during the forward calculations. The inverse solution was subsequently approached in the form of a set of dipolar sources demonstrating the smallest Euclidean norm (magnitude) of the modelled cortical currents. Co-registration of each MEG dataset with its corresponding MRI dataset was performed using an automated co-registration routine within MNE which aligns digitization points in the MEG headshape file with the fiducial points demarcated on the outer skin surface reconstruction of the MRI.

Temporally-constrained pair-wise functional associations between three left hemisphere temporoparietal regions (STG/BA22, SMG/BA40, ANG/BA39), and the IFG (BA44/45) were assessed. In addition, functional contributions made by activity in two visual association regions (the left fusiform gyrus/BA 37 and bilateral lateral occipito-temporal cortex/BA 19) to each of the temporoparietal and frontal regions were also explored. The anatomical extent of ROIs was determined automatically using the cortical map provided by Freesurfer (Desikan et al., 2006).

The MNE program outputs a current estimate measure for each cortical patch and each 4-ms time point. This measure was then used to compute the two dependent measures used in the analyses outlined next: (a) the average current across all patches defining each of the ROIs listed above and across all of the 4-ms time points comprising 14 successive 50-ms time bins (100–150, 150–200 ms, etc up to 800 ms) and, (b) the latency (in ms after stimulus onset) at which the estimated current reached peak amplitude within the entire recording epoch. Initially the temporal progression of regional activity was determined for each group by ranking ROIs according to peak latency. Next, a series of partial correlations were computed between average current in each of six left hemisphere ROIs presumed to play a key role in the brain mechanism for phonological decoding (STG, SMG, ANG, IFG, FUS, and LOC) and average current in all other regions. Correlations were computed for each pair of ROIs by controlling for the autoregressive effects of average current in the same two ROIs during the immediately preceding time bins (see Figure 1 for an illustration of the analytic strategy). For instance, when assessing the association between activity in STG at 200–250 ms and SMG at 250–300 ms, activity estimates in STG at 150–200 ms and in SMG at 200–250 ms were used as covariates. Degree of activity in the four primary target areas (STG, SMG, ANG, and IFG) was modelled in this manner in 13 successive bins (between 150 and 800 ms). Activity in the two visual association areas was considered between 100 and 750 ms, since it served only as a “predictor” of subsequent activity in the set of temporoparietal and inferior frontal regions. Correlation coefficients were evaluated at $p < .05$ in order to control for Type II error in this preliminary set of analyses (and include as many potential predictors in the multiple regression analyses). Finally, the set of regions whose activity significantly “predicted” subsequent activity in one of the four target ROIs were entered together into separate hierarchical, multiple regression models. These analyses examined the *relative* strength of the contribution of earlier activity in any of the six ROIs (four main regions [STG, SMG, ANG, IFG], LOC and FUS) to the strength of later activity in a particular target area. Age (in months) was also entered as a predictor in the first step of the analyses along with the autoregressive term for the dependent variable. The degree of activity in other ROIs was entered in the second step of the analyses (The ENTER method was adopted within each step).

Results

In-scanner performance indicated that the pseudoword reading task was not associated with ceiling effects given that mean naming accuracy was $82.5 \pm 16\%$ correct.

Temporal course of regional activity

Table 1 ranks the six left hemisphere ROIs in increasing order according to average peak latency in the corresponding source current density waveforms and demonstrates significant pair-wise differences. As shown graphically in Figure 2 the average spatiotemporal brain activation profile involved early activity in lateral occipito-temporal regions. This was followed after a significant delay by near-simultaneous peaks of activity in the fusiform and angular gyri. Subsequent activity peaks were noted in STG and SMG. Activity in the left IFG peaked last at a significant temporal delay following activity peaks in all other ROIs. On the basis of this information we focussed on statistical contributions to activity in the

four ROIs of interest during the first six 50-ms time bins for STG, ANG, and SMG (between 100 and 400 ms) and the first seven time bins for IFG (between 100 and 450 ms). In order to control for region-wise Type I error, a Bonferroni-corrected $\alpha = .008$ (.05/6 time windows) was set for evaluating the significance of R^2 change values ($\alpha = .007$ for IFG). If the R^2 change was deemed significant, regression coefficients were evaluated at $\alpha = .0125$ [.05/4 ROIs/predictors]. It should also be noted that collinearity did not appear to be an issue in the data, given that zero-order correlations between degree of activity in different ROIs at successive time windows ranged in moderate levels ($r < .56$ in all cases). Moreover, autoregressive effects rarely exceeded $r = .65$ (there two exceptions concerning early autoregressive effects where r equalled .68).

Functional associations between ROIs

Correlates of temporo-parietal activity—Correlational data presented in Tables 2 and 3 reveal a number of notable findings. Firstly, it appears that the degree of activity in each of the three temporo-parietal ROIs before 200 ms could not be accounted for by individual variability in the degree of activity in visual association, temporoparietal areas, or IFG. Secondly, partial correlation data in Table 2 do not show any evidence of contributions from IFG to later activity in temporoparietal areas (even at the uncorrected $\alpha = .05$, corresponding to a partial correlation coefficient $r = .23$) during the first 800 ms after stimulus onset. Instead, relatively early activity in temporoparietal cortices (150–250 ms) appears to be determined by activity taking place earlier within the same regions as indicated by autoregressive effects ranging between $r = .44$ and $r = .68$. There were some indications that activity in temporoparietal regions was determined, at least in part, by earlier activity in visual association cortices (first evident between 200 and 250 ms lasting throughout the next time window [250–300 ms]), as suggested by small to moderate correlation coefficients. Multiple regression analyses, however, did not support this conclusion: when indices of activity in visual association areas were entered together with autoregressive effects and age into predictor models, the only significant independent predictors of activity in STG, SMG, and ANG were autoregressive. Therefore, external inputs appear to account for negligible independent variance in temporoparietal activity that takes place up to 250 ms after stimulus onset. It should also be noted that we did not find any significant cross-correlations between ROIs after 450 ms.

Significant “external” contributions to STG activity were noted between 250–300 ms, made by earlier activity in the fusiform gyrus (at 150–200 ms). Reliable contributions to activity in ANG were noted much later (at 400–450 ms) made by earlier activity in the fusiform gyrus (between 350 and 400 ms). Finally, the only significant, independent “contribution” to SMG activity (at 250–300 ms) was served by earlier activity in STG (between 150–200 ms). It may be worth noting that less reliable associations were found for SMG (at 200–250 ms predicting later STG activity at 300–350 ms), STG (at 150–200 ms predicting later ANG activity at 250–300 ms), and lateral occipitotemporal cortex (at 200–250 ms predicting later ANG activity at 300–350 ms). These associations were not, however, associated with significant regression coefficients at the Bonferroni-corrected α level of .005. Therefore these activity indices may not be considered as significant independent predictors of the degree of subsequent activation in the superior temporal and angular gyri.

Correlates of inferior frontal activity—Activity in IFG does not appear to be influenced by direct inputs from occipitotemporal cortices in the left hemisphere at any point. The earliest significant external predictors of IFG activity (at 250–300 ms), originated in the angular gyrus and, subsequently (at 350–450 ms) in STG (between 250–300 ms). A significant association between activity in the angular gyrus (at 300–350 ms) and later activity in IFG (at 400–450 ms) was also found.¹

Discussion

The results of the present study replicated earlier MEG findings in children and adults with typical developmental histories for a regular progression of onset (Simos et al., 2007a,b) and peak latency of regional activity (Simos et al., 2011) from lateral to ventral occipitotemporal regions, followed by activity peaks in temporoparietal regions. The latter are, in turn, followed after a significant delay by an activity peak in the inferior frontal gyrus (pars opercularis). In the context of a three-letter pseudoword naming task designed to maintain the demands for phonological decoding low, yet require speeded processing under time-constraints, estimated cortical activity peaked within the first 450 ms after stimulus onset for the vast majority of participants in all target ROIs. Accordingly functional associations between ROIs were explored during a latency window starting at 100 ms post-stimulus onset and ending at 450 ms.

Solid directional arrows in Figure 3 denote reliable “forward” regional associations (i.e., between degree of activity in one left hemisphere ROI during a particular latency window and *subsequent* activity in a second ROI). The most notable findings can be summarized as follows: Significant contributions to the degree of activity in the superior temporal and angular gyri were made by earlier activity in the fusiform gyrus. The earliest latency bin during which significant regression coefficients were found with degree of activity in temporoparietal regions was between 200 and 250 ms after the onset of the pseudoword stimuli. The timing of occipitotemporal inputs to the temporoparietal area took place sufficiently early to permit signals from the former region (which includes the Visual Word Form Area; e.g., McCandliss et al., 2003) to determine the amplitude and latency of the activity peak in the superior temporal and angular gyri (activity peaked on average at 300, 330 and 360 ms in ANG and STG, and SMG, respectively). Human anatomical data point to an inferior branch of the arcuate fasciculus as the main fiber bundle conveying these signals (Catani, Jones, & ffytche, 2005; Epelbaum et al., 2008). This latency estimate is in agreement with previous MEG studies indicating that the earliest systematic dipolar activity in these regions during decoding and word reading tasks does not typically emerge before approximately 200 ms (Simos et al., 2005, 2007a,b; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999). The apparent lack of direct, independent inputs to the left SMG from visual association areas is perhaps more surprising given that this area shows robust differences between typical and impaired readers and a strong linear association with decoding ability in MEG data from the same cohort of students (Simos et al., 2011). Instead there was evidence of (probably) “bidirectional” associations between STG and SMG between 250 and 350 ms after stimulus onset. Given the nature of the activation task our findings are consistent with strong signalling between the two regions which probably serves to activate or construct sublexical phonological representations of the meaningless printed stimuli.

Moreover, the degree of activity in IFG between 250 and 450 ms appears to be determined, at least in part, by earlier activity in the angular and superior temporal gyri. Contributions from the left angular gyrus to IFG emerged earlier than those from STG and were more persistent in time than the latter. This finding is in agreement with accumulating evidence regarding the central role of the left angular gyrus in typical reading development, as indicated by reduced reading-related activity in this region in impaired readers (Temple et

¹An alternative approach to control for autoregressive effects would be to, first, compute the residuals of the correlations between activity in two successive time windows in the same ROI and, then, compute zero-order correlations between these residuals and activity in a different ROI during the later of the two time windows. As insightfully suggested by one of the reviewers of an earlier version of this work, this represents a more conservative method which could address potential collinearity issues. Using this method zero-order correlations between ROIs were reduced in all cases, although all cross-correlations computed after 250 ms listed in Table 2 still met the critical r value of .22 ($p = .05$).

al., 2001; Simos et al., 2007a; see also Eden & Zeffiro, 1998), strong associations between degree of activity in ANG and reading ability in non-impaired readers (Booth et al., 2003; Simos et al., 2011), and signs of reduced functional connectivity between the angular and inferior frontal gyri in impaired as compared to typical readers (Hampson et al., 1998; Pugh et al., 2000). We did not find evidence for direct contributions from ventral or lateral occipitotemporal regions to IFG at any latency window (even when using a relatively liberal partial correlation cut-off $r = .23$; $p < .05$ uncorrected). Although the two studies are not directly comparable, this finding is consistent with the lack of direct modulatory effects between the left fusiform gyrus and IFG reported by Cao et al. (2008; on the non-conflicting condition of a word rhyming task) and by Levy et al. (2009; during performance of a pseudoword reading task). A directional interaction between the fusiform and inferior frontal gyrus may emerge with age, however, as suggested by findings on adult skilled readers (Bitan et al., 2005). It is also possible that recruitment of a wider network of left hemisphere areas, in which ventral occipitotemporal areas play a central role, depends strongly upon specific task demands (Levy et al., 2009; Reinke, Fernandes, Schwindt, O'Craven, & Grady, 2008). In this context it has been suggested that decoding of non-lexical stimuli may not utilize direct occipito-frontal connections (Epelbaum et al., 2008). A further consideration, concerns the type of source localization method applied to MEG data. Whereas early event-related activity in IFG (i.e., within the first 200 ms after stimulus onset) modelled through equivalent current dipole or minimum norm estimates is not prominent, beamformer analyses, detecting oscillatory cortical activity, have repeatedly shown such early activity during reading (e.g., Pammer et al., 2004). More recently, this activity have been linked to phonological processing (Wheat et al., 2010) although the neurophysiological events triggering this activity have not yet been elucidated.

As mentioned above, the present data corroborate previous findings of a regular progression of activation peaks between occipitotemporal, temporoparietal, and inferior frontal regions, in the left hemisphere, among typical readers. Cross-correlational data support the pre-eminence of the presumed “feed-forward” (bottom-up) signalling. Feedback (top-down) inputs may take place but may not be sufficient (in intensity or spatial spread) to modulate the average activity in a given ROI. It is also possible that top-down influences are not very prominent in simple decoding tasks where processing is complete within the first few hundred milliseconds from stimulus onset. Tasks that require phonological-orthographic and semantic-syntactic integration may be more suitable to induce the need for fronto-temporal and/or fronto-parietal signalling (see for instance Bitan et al., 2006), which would be evident in regional degree of activity estimates such as those produced by MNE. It should also be considered here that the distinction between top-down and bottom-up contributions (in the anatomical sense) may be viewed in a different light when real-time temporal information is available. Thus, covariation of hemodynamic responses between an occipitotemporal and a temporoparietal region may reflect either a bottom-up effect taking place early during stimulus processing or a top-down contribution occurring much later (Dale et al., 2000).

For the majority of significant regression coefficients, a time lag of approximately 100 ms was implied between activity in the “source” and “target” areas. The time-lag estimate for significant cortico-cortical inputs may have been inflated, however, by the relatively coarse 50-ms time resolution permitted by the data reduction strategy used in the present study. Exploring the data at a finer time scale may be more productive although the issue of elevated Type I error rates is more apparent in this type of analyses. Another contributing factor may have been the use of the immediately preceding 50-ms latency bin in order to control for autoregressive effects which would inadvertently reduce the partial correlation coefficients between the degree of activity in different ROIs at temporally adjacent latency bins (i.e., at a time-lag of 50 ms). Complementary approaches in the frequency domain (coherence, synchronization likelihood, graph theory-based algorithms) applied on

minimum norm estimates of activation may also provide a viable source of connectivity information. The potential advantage of such approaches is their sensitivity to regional interdependencies which, at least in principle are not affected by task-related changes in the degree of regional activity. It may also be helpful to apply the analytic procedure used in the present study to regional activation data derived from beamformer methods which tend to produce more “focal” (i.e. regionally constrained) cortical activation maps (Salmelin & Kujala, 2006).

It should be noted that the results presented here apply to a specific type of stimulus which was initially selected in order to accommodate students with word-level reading difficulties as part of a larger longitudinal study. In doing so demands for graphemic and phonological processing were kept low, possibly affecting the generalization of findings to the cortical mechanism responsible for phonological processing at large. Future research should extend this to longer pseudowords constructed on the basis of different word origins of English, which differ in the phonological, orthographic, and morphological interrelationships. Our approach attempted to control for the tendency of distributed source modelling approaches, such as MNE, to produce highly correlated maps especially for adjacent cortical regions. This method ventured to overcome this potential problem by examining time-lagged regional associations while controlling for autoregressive effects. It has the advantage of taking into account real-time temporal information to estimate directionality of functional associations. However, it may be considered as only a preliminary step in constructing a comprehensive functional connectivity model since it does not take into account mediating effects or common contributions (see for instance, Guye, Bartolomei, & Ranjeva, 2008; Marelec et al., 2008). The former could account for associations between target areas A and B mediated through signalling from A to a third area, C, which in turn projects to B. Such an indirect pattern of regional connectivity has been recently suggested for inputs from the angular gyrus to SMG via the lateral occipitotemporal region (Carreiras et al., 2009). The latter is conceivable if C is responsible for an early input to A followed by a similar, but later input to B. This goal could be pursued through multivariate methods such as structural equation modelling (Kim & Horwitz, 2009; Levy et al., 2009) and the related method of Dynamic Causal Modelling (Friston et al., 2003; Mechelli et al., 2002), and conditional Granger Causality (Zhou, Chen, Ding, Wright, Lu, & Liu, 2009). In this respect additional cortical regions should also be examined, potentially accounting for increased amounts of variability in activation in key areas of the brain mechanism for reading. For instance, activity in right hemisphere homologous regions has been shown to closely covary with activity in the left angular gyrus in skilled readers (Carreiras et al., 2009). These multivariate approaches are also more suitable for examining the effects of age on the pattern of functional cortical associations. At present the (wide) age range of participants, which poses a potential threat to the external validity of the results, was addressed by simply including age as a covariate in the multiple regression analyses. In doing so, however, some of the weaker associations may have been reduced to non-significance requiring multigroup analyses to show interactions between age and strength of specific functional cortical associations.

Acknowledgments

This research was supported in part by grant P50 HD052117 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NICHD or the National Institutes of Health.

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Highlights

- The study includes a large sample of elementary and middle school typical readers
- MEG explores relative timing of neurophysiological activity during decoding
- Activity progressed from visual association to temporoparietal to inferior frontal cortex
- Functional associations between cortical regions were assessed in real-time
- Result indicated bottom-up effects during the first 500 ms of pseudoword reading

Figure 1.

Schematic examples of correlational analyses on time-dependent degree of neurophysiological activity in two of the primary target ROIs (left IFG and SMG) and in the left lateral occipitotemporal cortex. Traces represent the MNE-estimated source current density waveform averaged across all cortical patches comprising each ROI. Each dotted line indicates the partial correlation computed between degree of activity in a pair of ROIs at successive latency windows. For instance, [a] indicates the regression of activity in IFG between 300 and 350 ms over preceding activity in SMG (between 250 and 300 ms) while simultaneously controlling for activity in IFG in the 250–300 ms window and activity in SMG in the 200–250 ms window. Note that only the first few and the latest of the latency

bins considered in the analyses are marked in the drawing. Abbreviations; IFG: Inferior Frontal Gyrus, SMG: Supramarginal Gyrus, LOC: Lateral occipitotemporal cortex.

Figure 2.

Relative timing of activity peaks across six left hemisphere ROIs. Vertical bold lines indicate group means, boxes represent interquartile ranges, and horizontal bars indicate the range of individual values. Abbreviations; IFG: Inferior Frontal Gyrus, SMG: Supramarginal Gyrus, STG: Superior Temporal Gyrus, ANG: Angular Gyrus, FUS: Ventral Occipitotemporal cortex (fusiform gyrus), LOC: Lateral occipitotemporal cortex.

Figure 3.

Schematic rendering of significant regression coefficients for pairs of ROIs. The beginning of each line represents activity at an earlier time bin in a particular ROI (usually by 100 ms) “predicting” degree of activity at a subsequent time bin in a different ROI (indicated by the head of the arrow). Time-dependent regional associations shown here are independent of autoregressive effects and of “forward”, concurrent contributions made by other ROIs. Dotted lines: significant coefficients at $p = .05$; solid lines: Significant coefficients at $p = .008$ (uncorrected).

Table 1

Significant pairwise differences (*corrected $p = .003$) in peak latency for regional source-density waveforms.

	LOC	FUS	ANG	STG	SMG	IFG
LOC						
FUS	*					
ANG	*					
STG	*	*	*			
SMG	*	*	*	*		
IFG	*	*	*	*	*	*

Table 2

Partial correlation coefficients between the degree of activity in the left STG, SMG, ANG, and IFG and earlier activity in these ROIs, and also in ventral and lateral occipitotemporal cortices.

ms	Target ROI			
	STG	SMG	ANG	IFG
150–200	(.68) SMG _{100–150} (.31)	(.68) FUS _{100–150} (.25) STG _{100–150} (.27)	(.53)	(.57)
200–250	(.52)	(.42) ANG _{150–200} (.30)	(.44) FUS _{100–150} (.34)	(.50) † STG _{100–150} (.32) SMG _{100–150} (.29)
250–300	(.59) LOC _{150–200} (.47) † FUS _{150–200} (.43)	(.60) LOC _{150–200} (.43) † FUS _{150–200} (.33) † STG _{150–200} (.32)	(.56) LOC _{150–200} (.27) FUS _{150–200} (.25) † SMG _{150–200} (.33)	(.59) LOC _{150–200} (.39) FUS _{150–200} (.34) ANG _{150–200} (.46)
300–350	(.54) † SMG _{200–250} (.32)	(.67)	(.64) † LOC _{200–250} (.29)	(.64)
350–400	(.60)	(.55)	(.45)	(.60) † STG _{250–300} (.37)
400–450	(.58)	(.61)	(.57) † FUS _{350–400} (.42)	(.54) † ANG _{300–350} (.33)

Significant partial correlation coefficients ($p < .05$), controlling for autoregressive effects on each of the two associated variables, are given in parentheses. The autoregressive effect for each target variable is given in italics (partial correlation coefficient between the target variable and activity in the immediately preceding time window, controlling for activity in earlier time windows). Significant independent predictors of later activity (when all potential predictors entered together into the model) are indicated by crosses (detailed results for these analyses are presented in Table 3; all autoregressive effects remained significant predictors of later activity in the multiple regression analyses at $p < .0001$).

Table 3

Summary of results of hierarchical multiple regression analyses accounting for activity in the four target ROIs between 150 and 450 ms.

ms	Dependent Variable			
	STG	SMG	ANG	IFG
150–200	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch} ns$
200–250	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch}=07, F(1,58)=6.19, p=.01^c$ $STG_{100-150}: \beta=.25, t=2.48, p=.01$
250–300	$R^2_{ch}=10, F(1,61)=13.75, p=.0001^a$ $FUS_{150-200}: \beta=.35, t=3.71, p=.0001$	$R^2_{ch}=11, F(3,59)=4.65, p=.006^b$ $STG_{150-200}: \beta=.33, t=3.40, p=.002$	$R^2_{ch}=06, F(2,62)=4.42, p=.016^d$ $STG_{150-200}: \beta=.20, t=2.13, p=.04$	$R^2_{ch}=15, F(2,58)=9.37, p=.0001^e$ $ANG_{150-200}: \beta=.32, t=3.16, p=.003$
300–350	$R^2_{ch}=03, F(1,63)=4.57, p=.04^f$ $SMG_{200-250}: \beta=.20, t=2.14, p=.04$	$R^2_{ch} ns$	$R^2_{ch}=04, F(1,62)=5.23, p=.026^g$ $LOC_{200-250}: \beta=.21, t=2.29, p=.025$	$R^2_{ch} ns$
350–400	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch}=08, F(1,58)=9.30, p=.003^h$ $STG_{250-300}: \beta=.31, t=3.10, p=.003$
400–450	$R^2_{ch} ns$	$R^2_{ch} ns$	$R^2_{ch}=10, F(1,62)=18.93, p=.0001^i$ $FUS_{350-400}: \beta=.37, t=4.35, p=.0001$	$R^2_{ch}=09, F(1,58)=12.79, p=.001^k$ $ANG_{300-350}: \beta=.32, t=3.70, p=.001$

Notes. The list of independent variables entered into each model is given in the corresponding cell in Table 1 (in addition to age in months and the autoregressive term for the dependent variable). R^2_{ch} : Amount of change in R^2 when independent variables representing earlier activity in *other* ROIs were entered in the model (significance evaluated at $\alpha = .007$ [.05/7] for IFG and $\alpha = .008$ [.05/6] for the remaining ROIs). Here only variables making significant independent contributions are listed with their respective standardized regression coefficients (evaluated at $\alpha = .0125$ [.05/4]). Non-significant results are shown in italics. Final Adjusted R^2 when all predictor variables were entered together in the model were,

- a : .55,
- b : .60,
- c : .46,
- d : .53,
- e : .51,
- f : .55,
- g : .57,
- h : .53,
- i : .67,

k; 63.

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