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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.

1. 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 thought to be mediated by neurophysiological processes operating in the ventral occipitotemporal 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, Breier, Fletcher, Bergman, & Papanicolaou, 2000; Simos et al., 1999; Simos, Breier, Wheless, et al., 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 et al., 2008; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Sandak et al., 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, Horwitz, Rumsey, and

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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, Stephan, Mechelli, & Friston, 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, Lu, Burman, and 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, Wood, Lu, Houk, and Bitan (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 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, 2001), 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; Simos, Fletcher, Sarkari, Billingsley, et al., 2007; Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007). 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., Demonet, Taylor, & Chaix, 2004; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Maisog et al., 2008; Schlaggar & McCandliss, 2007; Shaywitz, Lyon, & Shaywitz, 2006), 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 (Cao, Bitan, Chou, Burman, & Booth, 2006; Eden & Zeffiro, 1998; Hoeft, Meyler, et al., 2007; Hoeft, Ueno, et al., 2007; Maisog et al., 2008; Shaywitz et al., 2002; Temple et al., 2001; van der Mark et al., 2009) and neuromagnetic studies (Simos, Breier, Fletcher, et al., 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 nam-