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Distorted cortical networks in dislexia: findings using Magnetoencephalography (MEG).

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Resumen: *En niños disléxicos se sospecha un déficit funcional del circuito cerebral implicado en algunos de los procesos que acaecen cuando aprenden la relación entre la conversión del grafema al fonema. No ha sido hasta recientemente cuando se ha obtenido información sobre el funcionamiento de este circuito en los estadios precoces de la adquisición lectora. Tres han sido los estudios que han servido para abordar factores clave en esta condición, mediante el empleo de la Magnetoencefalografía (MEG) en la Universidad de Texas –Houston. El primer estudio, en el que se incluyeron 30 niños en edad pre-escolar en riesgo de padecer problemas lectores y 15 controles sin riesgo de padecerlos, se comprobó que el circuito neuronal aberrante característico en los problemas lectores es aparente en los primeros estadios de la adquisición de habilidades lectoras. Un grupo de estos niños se estudiaron un año después con el mismo procedimiento en un segundo estudio. Los niños en riesgo de padecer problemas lectores mostraron un perfil de activación cerebral destacado que predecía diferencias individuales en las pruebas de habilidades lectoras. Un tercer estudio mostró una clara tendencia a la corrección del patrón de activación cerebral anormal tras una intervención cognitiva intensiva de los niños. Estos hallazgos son consistentes con la perspectiva de que la dislexia constituye un déficit funcional en el circuito neuronal implicado en la conversión del grafema al fonema, y que es susceptible de ser corregido con una intervención adecuada.*
Palabras Clave: *Magnetoencefalografía, MEG, dislexia, conciencia fonológica.*

Abstract: *In dyslexic children a functional deficit in the brain circuitry supporting some of the cognitive operations taking place while they learn how the printed words maps onto spoken language is suspected. Until recently, however, no information existed regarding the functional status of this circuit during the early stages of reading acquisition. In the context of three studies we sought to address key issues in the pathophysiology of this condition using*

Magnetoencephalograhy (MEG) at the University of Texas-Houston. The first study, including 30 kindergarten children at risk for developing reading problems and 15 not-at-risk controls, ascertained that the aberrant neural circuit that underlies reading problems appears to be present in the initial stages of reading acquisition. A subset of these children were retested a year later using identical procedures in a second study. Children in the at-risk group showed the most prominent changes in brain activation profiles and successfully predicted individual differences in the growth of reading skill measures. The results of a third study showed clearly that the aberrant activation profile can be normalized following intensive behavioral instruction. These findings are consistent with the view that dyslexia represents a functional deficit in the neural network that mediates the conversion of print to sound, which is amenable to change given adequate instruction.
Key words: *Magnetoencephalography, MEG, dyslexia, phonemic awareness.*

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Introduction

Regional specialization for processes involved in reading develops on an advanced network of brain areas involved in linguistic operations. This network shows signs of specialization soon after birth (Entus, 1977; Hahn, 1987; Hiscock, 1988; Molfese & Betz, 1988), although irreversible commitment of various component areas may not be complete until puberty (effects of lesions, potential for plasticity). Reading, on the other hand, is a relatively late achievement in the course of human development, and depends on skills that do not appear to be directly related to those normally involved in understanding spoken language, such as phonological awareness (Liberman, 1998).

Little is known regarding the development of neurophysiological processes associated with reading acquisition. Nonetheless, the spatial extent of task-specific cortical engagement is expected to change with time during acquisition of any new skill (Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar 1998; Poldrak Desmond, Glover, & Gabrieli, 1998). Therefore, a progressive increase in the degree of left hemisphere specialization of these regions for reading-related processes is expected, contrasting with oral language where hemispheric representation appears to be established very early. However, if specialization has resulted in a functionally aberrant brain circuit for reading, is it possible to change it to a circuit capable of sustaining a functional level of reading skill? An alternative hypothesis postulates the existence of a critical period for the acquisition of reading skills, beyond which the brain circuit supporting this function is virtually incapable of plasticity.

A direct approach to study cortical specialization is to record brain activity during performance of tasks designed to engage the cognitive operations under study. Describing the cerebral mechanisms that support reading involves clarifying the exact temporal characteristics and anatomical distribution of neurophysiological activity that reflect inter-neuronal signaling within and between different brain areas. This goal requires:

- Information regarding brain areas that show increased levels of neurophysiological activation during reading tasks;
- Real-time data regarding the temporal course of regional activation;
- Information on how brain activity measures relate to individual performance in these tasks;
- And, Independent confirmation, preferably from invasive functional brain mapping, that areas activated during a particular task are essential for the performance of that task.

Functional imaging studies of individuals with reading disabilities (RD) consistently report decreased activation in the left temporoparietal areas during tasks involving phonological analysis of print (Rumsey, Andreason, Zametkin, *et al*., 1992, Rumsey, Nace, Donohue, *et al*,. 1997; Shaywitz, Shaywitz, Pugh, *et al*., 1998). Studies using FMRI have demonstrated that in reading tasks that require phonological analysis, adults with persisting reading difficulties engage the posterior brain regions including the angular gyrus, the superior temporal gyrus and striate and extrastriate regions of the occipital lobe to a lesser extent than controls (Shaywitz, *et al*., 1998). Moreover, when compared with non-impaired readers, adults with reading problems may show compensatory hemodynamic changes in tasks that require phonological analysis of print in right temporoparietal areas and in the inferior frontal gyrus (Shaywitz, *et al*., 1998). The presumed reliance on the anterior circuit has not been found in children with dyslexia (Shaywitz, *et al*., 1998). Studies using PET agree only in part with these findings. Gross-Glenn, Duara, Barker, *et al*. (1991) and Rumsey, *et al*. (1992, 1997) found reduced activity in left temporoparietal areas in adults with RD during reading tasks. Both studies, however, failed to find evidence of increased involvement of the anterior circuit in dyslexia.

Functional imaging methods, like FMRI that measure changes in hemodynamics lack the requisite resolution to show the sequence of regional activation in real time. These modalities are, therefore, forced to derive evidence regarding functional interactions between different brain regions that participate in the mechanism of reading from cross-correlations in the task-related degree of activation among active regions. Some evidence of reduced functional connectivity between the angular gyrus and temporal lobe areas in the left hemisphere in adults with dyslexia has been found using this method (Pugh, Jenner, Mencl, *et al*., in press). Dyslexic readers consistently demonstrated disruption in connectivity in the left hemisphere during tasks that make varying demands on phonological processing; with no dysfunction noted when visual-orthographic coding was required. The authors concluded that when heavy demands for phonological processing are made by the experimental task, a reading circuit that involves right hemisphere areas is engaged to potentially compensate for the disrupted left hemisphere circuit.

The latest in non-invasive functional imaging techniques is the method of magnetoencephalography (MEG), also known as Magnetic Source Imaging (MSI). It records the magnetic flux associated with electrical currents in activated sets of neurons. It allows tracking of brain activity in real time but, unlike evoked electrical potentials, the sources of this activity can be accurately estimated as they are not distorted by differences in conductivity between the brain, skull and scalp. Deduction of the sources from the measured magnetic field distribution is simple, and both the spatial and temporal aspects of the activity can be determined with remarkable accuracy (0.1 to 1 cm and 1 msec respectively). The location of these activity sources are estimated and projected onto the structural images of the brain

(MRI), which allows for visualization of the activated brain regions (Papanicolaou, 1998). The procedures for imaging with MSI can be summarized as follows: Presentation of auditory or visual stimuli result in regional increases in neuronal signaling. Changes result in the intra- and extracellular flow of ions in large neuronal aggregates which, in turn, generate electrical currents and magnetic fields. With recurring presentations of stimuli, these signals can be recorded as evoked potentials and event-related fields (ERFs) on the head surface. ERFs, much like evoked potentials, are waveforms that represent temporal variations in brain activity time-locked to the presentation of stimuli. Some of the waveforms are noted to occur consistently across different experimental conditions and are known as “components”. There are two basic components: (a) early, extending up to 150 ms following stimulus onset; and (b) late, lasting several hundred milliseconds after stimulus onset. Early components reflect activation of the primary sensory cortex (Nakasato, Kumabe, Kanno, *et al*., 1997; Seki, Nakasato, Fujita, *et al*., 1996). Late components have been shown to reflect activation of the association cortex (Rogers, Baumann, Papanicolaou, *et al*., 1991; 1993; Simos, Basile, & Papanicolaou, 1997).

MSI fulfills the criteria for functional imaging studies of higher cognitive functions proposed above, as it possesses adequate temporal and anatomical resolution. Moreover, there is ample evidence on the concurrent validity of MSI protocols. For example, MSI-derived hemispheric asymmetries were in excellent agreement in the degree of regional activation associated with auditory word recognition, with the results of a standard invasive procedure used clinically to determine hemispheric dominance (Wada test) in over 80 consecutive epilepsy patients (Breier, Simos, Zouridakis, *et al.*, 1999; Maestu *et al*., in press; Papanicolaou *et al*., in press). In addition, there was precise concordance between MSI-derived maps of language-specific activity within the dominant hemisphere, and the results of direct electrocortical stimulation for the exact spatial localization of the receptive and expressive language cortex (Castillo, Simos, Venkataraman, *et al*., 2001; Simos, Breier, Fletcher *et al*., 2000; Simos, Papanicolaou, & Breier 1999). Moreover, MSI data regarding the timing of activity in left hemisphere temporal lobe areas correlate strongly with individual performance (reading speed) (Simos, *et al*., 2000).

In our laboratory all MSI recordings are made with a multichannel neuromagnetometer (4-D Neuroimaging, Magnes 3600) consisting of 248 magnetometers arranged to cover the entire head. It is housed in a magnetically shielded chamber used to reduce environmental noise that may interfere with the recording of biological signals. As the typical recording session, during which the participant must remain still, rarely exceeds 10 minutes, it is possible both to repeat measurements to establish reliability of results, and to test very young children. Until recently, all functional brain imaging (including all MSI studies) of the brain mechanisms for reading, has been performed long after the potentially critical period of reading acquisition has lapsed. No data was available on the emergence of either the normal or the aberrant brain circuits associated with learning to read. The prevention of reading problems is more desirable and cost-effective than lengthy intervention programs following a delayed diagnosis. Using MSI, the studies described below attempt to map brain regions involved in complex cognitive functions in individual patients as a first step in the early diagnosis of dyslexia. Existing functional imaging studies rely on group data for statistical analysis and interpretation.

The general outline of the spatio-temporal profile of neurophysiological activity associated with the brain mechanism that supports reading has been described by several MSI studies with both adults and children during the performance of both silent and overt reading tasks (Breier, Simos Zouridakis & Papanicolaou, 1998, 1999b; Simos, Breier, Fletcher, *et al*., 2001). In adult readers this profile features initial activation in the occipital visual areas (within the first 150 ms after the onset of the printed stimulus), followed by activity in the occipito-temporal and ventral temporal cortices (between 150-300 ms predominantly in the left hemisphere) and finally by activation of posterior superior temporal, inferior parietal and inferior frontal regions (again, predominantly in the left hemisphere). The spatiotemporal activation profile observed in older children without reading difficulties is similar to the one found in adults with one notable exception, namely the lack of the hemispheric asymmetry (left > right) in the degree of activation of visual association areas in the ventral surface of the temporal lobe.

The present paper reviews preliminary evidence obtained with the use of MSI that bears on three interrelated issues: 1) What is the developmental course that leads to the establishment of the activation profile seen in older children and adults? 2) What is the developmental course that leads to the establishment of the aberrant activation profile seen in older children with reading difficulties? 3) To what extent can intervention alter the developmental course of the aberrant activation profile seen in dyslexic children?

Study 1. Emergence of activation profiles specific to reading

In our first study we examined whether the aberrant brain activation profile observed in older children with dyslexia is already present during the early stages of reading acquisition. Thirty "at-risk" kindergarten children, who had not mastered knowledge of letter sounds and were considered to be at risk for developing reading difficulties, were compared to 15 children that mastered this essential skill. Brain activation scans were obtained at the end of the kindergarten year while each child was performing a letter-sound pronunciation task. At-risk children displayed a markedly different activation profile than not-at-risk children. This aberrant profile was characterized by the lack of engagement of the posterior portion of the left superior temporal region, and an increase in activation in the homologous right hemisphere region (see Figure 1). This profile is very similar to that observed consistently in older children with severe reading difficulties (Simos *et al.*, 2000a, b). Timing data, present in Figure 1 as well, indicate that children in the at-risk group engaged the right superior temporal area soon after the letter stimulus was presented, but that activity in this area may not be sustained long enough to ensure access to the letter-sound representation.

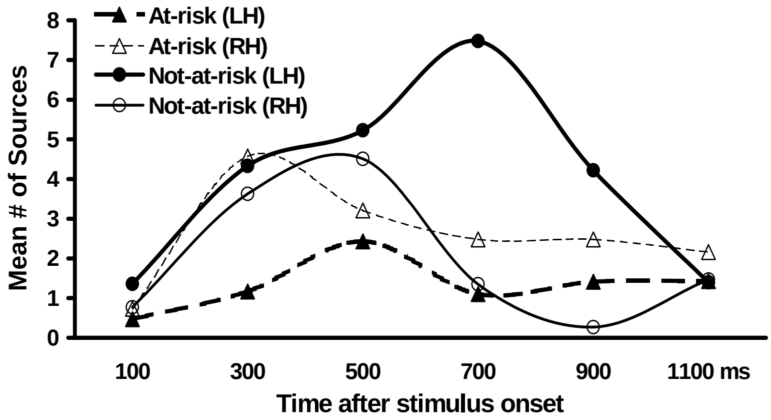

Figure 1. Upper panel: MSI activation profiles from a typical at-risk child (upper set of images), and from a child in the not-at-risk group (lower set of images), during the letter-sound task. Note the abundance of activity in the left superior temporal gyrus in the latter case and the scarcity of such activity in the former case. Children in the two groups are indistinguishable with respect to activity in any other brain area. Lower panel: Average degree of activity in the left (solid markers) and right superior temporal gyrus (white markers) for the two groups of children as a function of time after the onset of the visual letter stimuli

Study 2. Growth of activation profiles specific to Reading

A subset of the children that participated in Study 1 were tested one year later after they had completed first grade. Brain activation profiles were obtained using identical procedures as in the previous year. Data from 10 children in the at-risk group and six children in the not-at-risk group are summarized in Figure 2. A significant developmental change in the degree of left hemisphere temporoparietal activity was apparently in the at-risk group. This effect was still evident when regional activity was normalized with respect to total brain activity in order to control for potential changes in overall brain activation with maturation (see Figure 3). The amount of increase in the relative degree of left temporoparietal activity was a significant predictor of the degree of change in letter-sound knowledge between kindergarten and first grade, $F(1, 15) = 17.43$, $p < .001$, Adjusted R2 = .523. Adding the amount of change in right temporoparietal activation did not improve the regression function, $F(1, 15) = 9.75$, $p < .003$, Adjusted R2 = .539.

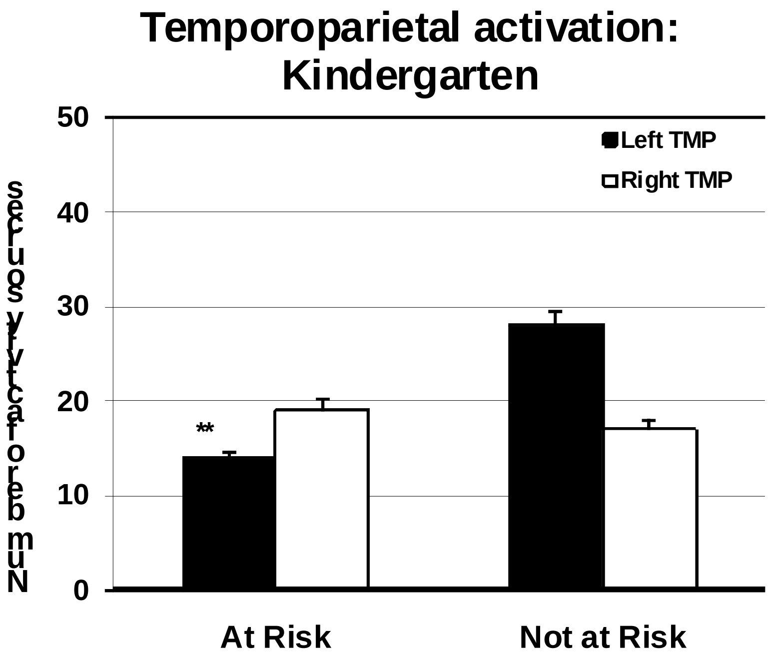

Figure 2. Average degree of activity in the left and right superior temporal gyrus in the group of children at risk for developing reading problems and in the not-at-risk group. Longitudinal data from a total of 16 children were obtained at the end of kindergarten (upper panel) and one year later at the end of first grade (lower panel). The asterisks indicate the statistically significant ($p < .01$) increase in left temporoparietal activation in the group of children at risk for developing dyslexia.

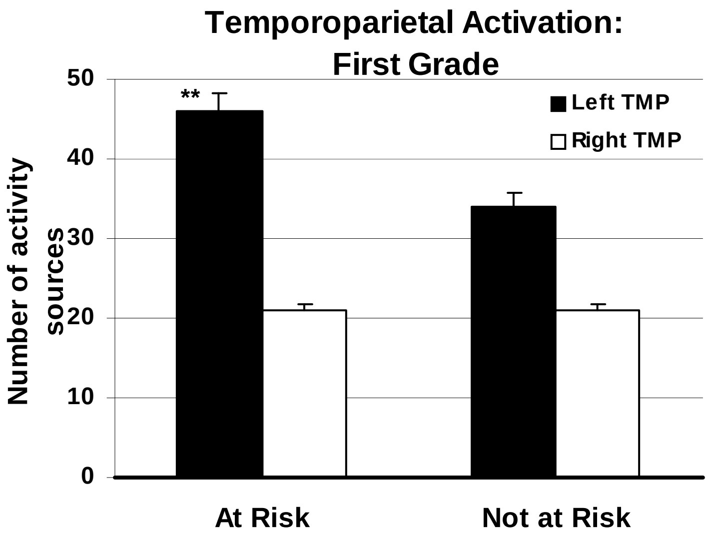

Figure 3. Degree of activity in the superior temporal region adjusted with respect to activity in the entire brain as a function of grade. Notice the dramatic increase in left superior temporal activity and the corresponding decrease in the right superior temporal region that is especially pronounced in children who had not mastered key pre-reading skills at the end of kindergarten (At-risk group, dark lines). The change in the degree of normalized temporoparietal activation was hardly noticeable in the group of children who had mastered these skills (Not-at-risk group, red lines). Vertical bars represent standard error.

Study 3. Plasticity of reading-related activation profiles in older dyslexic children

The hypothesis for the third and final study of this series was, that if difficulty in mentally converting print into sound representations is associated with failure to engage the left temporoparietal region, then intense training focusing on the development of these skills should lead to the restoration of function to this area and to significant improvement in reading skills. Eight children (aged 8-16 years) were scanned while performing a pseudoword reading task before and after a reading intervention (Simos, Papanicolaou, Breier, *et al.*, 2000a). Intervention was conducted using intensive reading instruction programs that focused on the development of phonological decoding skills, and consisted of 80 hours of one-to-one instruction (Lindamood Phonemic Sequencing and Phono-graphix programs). Before enrolling in the intervention program, all eight children showed the typical "dyslexia-specific" profile featuring little or no activity in left superior temporal areas and strong activation of homotopic areas in the right hemisphere (see Figure 4). In all cases, the intervention resulted in marked improvement in phonological decoding abilities, paired with a dramatic increase in left superior temporal lobe activation and a moderate decline in activation of the corresponding right hemisphere areas.

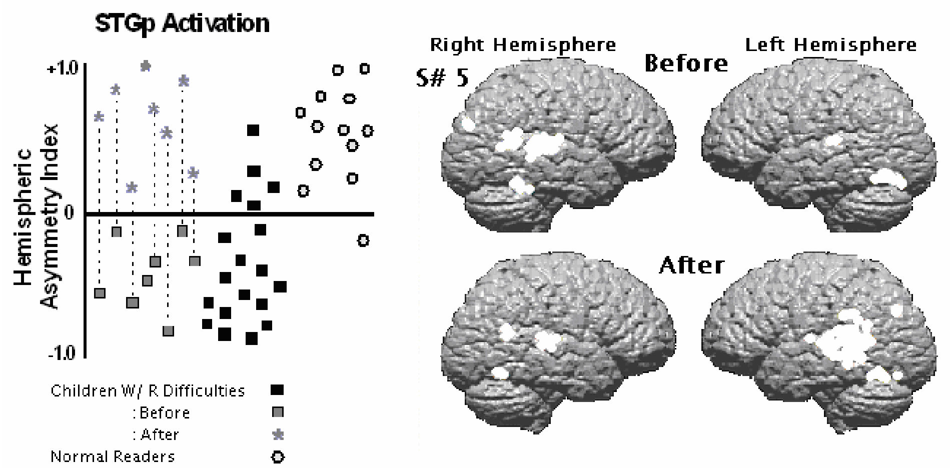

Figure 4. Top: The distribution of individual hemispheric asymmetry indices (Left –Right) / (Left + Right) for the degree of activation in the superior temporal gyrus for children who experience severe reading difficulties (squares) and fluent readers (open circles) during performance of the pseudoword reading task (see Figure 1). The scores of the eight children in the former group, who successfully completed an 8-week intensive instruction program, are represented by stippled squares (before instruction) linked with asterisks (after instruction). Note the shift of asymmetry indices from negative to positive values reflecting the marked increase in left superior temporal gyrus activation in all cases. All eight children showed dramatic improvement in their phonological decoding skills after receiving 8 weeks of intensive remedial instruction. Bottom: Individual activation maps from a representative case, a 9-year old child, scanned before and after instruction using the Phonographix program.

Conclusions and implications.

Based on the findings from the three studies outlined above, the following conclusions can be derived. First, the vast majority of children with serious reading problems show, during engagement in reading tasks, a distinct brain activation profile that is uncommon among children who have never experienced reading difficulties. It remains to be seen if this profile is independent of other conditions, such as attention deficit/hyperactivity disorder, that show a high degree of comorbidity with dyslexia. Second, this profile is observed in a variety of tasks that involve phonological decoding regardless of whether the task involves reading of real words or pseudowords. Third, it appears that neurophysiological activity in left superior temporal regions revealed by MSI reflects the engagement of brain operations that are indispensable components of the brain mechanism for reading. If these operations are not engaged properly, as in the case of dyslexia, reading performance and the capacity to acquire reading skills is severely compromised. There are strong indications that these operations are predominantly involved in phonological processing of print. Fourth, the aberrant neural circuit that underlies severe reading problems in older children with dyslexia appears to be present during the early stages of reading acquisition, at a much earlier age than previously believed. Fifth, individual differences in the degree of specialization of the left temporoparietal region account for a significant proportion of individual variability in mastering the alphabetic principle. Sixth, systematic reading instruction that promotes the development of phonological awareness and decoding skills can drastically alter the aberrant activation profile found in children with dyslexia.

These findings have important implications for current views regarding the pathophysiology and optimal management of dyslexia. Brain imaging data from kindergarten children prove that it is possible to detect signs of an aberrant brain circuit responsible for reading before the level of actual ability in reading is established. The fact that neural signs of dyslexia are present very early in the reading acquisition process highlights the importance of early intervention.

Our findings are consistent with current cognitive models of reading acquisition and dyslexia, pointing to the critical role of basic knowledge of the correspondence between letters and sounds in learning to read. Our results also concur with views of reading as a trait that is normally and quantitatively distributed in the population. Thus, reading difficulties most likely represent variations in normal development as opposed to a specific pathological condition. Moreover, reading difficulties in many individuals can be overcome by intervention that is sufficiently intense. When successful intervention occurs, our evidence suggests that neural systems are altered and that these neural systems are much more plastic than was believed in the past.

Finally, the results have important implications for views of neural plasticity as well as views of how environmental factors impact the brain. According to one hypothesis, recruitment of brain areas already specialized for linguistic operations occurs naturally during the early stages of reading acquisition. This hypothesis predicts that little, if any, change is evident in the degree of activity in left temporoparietal regions as children master the alphabetic principle. According to an alternative hypothesis, recruitment of cortical areas that are already specialized for linguistic processing is a time-intensive process that requires extensive experience with print. This hypothesis predicts a significant increase in the engagement of left temporoparietal areas during the primary grades. Our data (Studies 1 and 2) support the former hypothesis. It appears that the majority of children in kindergarten who have been exposed to print show signs of specialization of cortical areas which in older children and adults are involved in mapping print to phonological representations. Such areas as the superior temporal and the supramarginal gyri in the left hemisphere are also involved in the phonological processing of aural language, as predicted by this hypothesis. Even children who initially experience difficulties in mastering essential skills that are precursors of reading ability (such as knowledge of letter sounds) typically show dramatic changes in the degree of commitment of left temporoparietal areas. When tested at the end of first grade, brain activation profiles of these children become virtually indistinguishable from those of children never considered to be at risk for developing reading problems. It should be noted, however, that virtually all children who participated in Studies 1 and 2 received direct instruction during the period between the two MSI scans. It remains to be seen if children not at risk for developing reading problems will show the same maturational profile if they are not taught the alphabetic principle directly.

Although preliminary, the data presented here concur with the view that direct, and not necessarily intensive, instruction in the alphabetic principle is sufficient to promote development of a "normal" brain circuit that supports reading. However, in a smaller proportion of children this process does not take place in the regular classroom and the brain circuit that is specialized for reading does not emerge. In those cases, intense remedial instruction that promotes the development of decoding and word recognition skills may jumpstart the normal maturation process of functional brain specialization. Although it is common to describe the children and adults who are poor readers as "disabled", the fact that our preliminary data suggests that the brain activation profiles associated with poor reading are malleable and change with instruction, may indicate that instruction plays a significant role in the development of neural systems that are specialized for reading.

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