



The Use of Neuronal Response Signals as Early Biomarkers of Dyslexia

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Abstract

Objectives Brain imaging techniques have broadened our understanding of structural and functional properties of neuronal networks in children with developmental disabilities. The present work examines current models of neuronal response properties implicated in dyslexia and reading difficulties.

Methods This review analyzes the use of functional techniques (fMRI and EEG) employed in the assessment of neuronal markers associated with reading ability.

Results Neuro-imaging studies have provided evidence of neuronal networks involved in the emergence of reading fluency. Using this information, it is now possible to employ physiological assessments in the screening of reading ability before behavioral evaluations can be conducted.

Conclusions Analyses of neuro-imaging studies show that abnormal neuronal activation in specific brain areas can be used to help identify reading impairments in children. These neuronal assessments permit earlier identification of dyslexia than those requiring behavioral assessments.

Keywords Neuroimaging · Dyslexia · Educational outcomes · Reading · Neuronal markers

Dyslexia is a disorder that impairs the development of literacy despite normal intelligence, sensory processing, and educational training (American Psychiatric Association [APA], 2022). While the diagnostic tools of dyslexia have been governed by behavioral and genetic profiles (Cardon et al., 1994; Erbeli et al., 2022; Gialluisi et al., 2021; Shaywitz, 1998), neurophysiological and neurovascular studies have consistently revealed structural and functional variations in dyslexic individuals (Chyl et al., 2021; Liebig et al., 2020; Norton et al., 2015). These observations suggest that the evaluation of neurophysiological markers may provide constructive information during diagnostic assessments of dyslexia in pre-literate children.

Early identification of students at-risk of developing dyslexia has the potential to improve learning and life-long professional outcomes for millions of children worldwide. This proposal is supported by comparisons of behavioral outcomes following early and late reading mediations (Sanfilippo et al., 2020). Specifically, reading interventions in

early-childhood have been associated with stronger academic benefits than those introduced as remediation efforts later in life (Scammacca et al., 2015; Wanzek & Vaughn, 2007). Developmental properties of neuronal networks explicate this discrepancy by implicating rapid changes in neuronal connectivity that are exclusively present during early childhood (Fandakova & Hartley, 2020; Greenough et al., 1987; Pleisch et al., 2019). In this model, experience dependent plasticity shapes the organization of neuronal networks linked to reading proficiency early in development. Despite the well-established properties of sensitive periods in childhood (Zeanah et al., 2011), detection of reading disabilities remains largely limited to behavioral measures that inevitably delay interventions to less malleable periods of neuronal plasticity in life. Therefore, identification of pre-literate children at-risk of developing dyslexia may improve the outcomes of mediations by allowing clinicians to commence interventions during optimal neurodevelopmental periods in early childhood. Furthermore, efforts to compare assessments of cognitive domains to academic achievement, detecting patterns of strengths and weaknesses, or monitoring how children respond to intensive reading interventions as a means of identifying dyslexia have produced limited results in the research literature (Whittaker & Burns, 2019).

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These findings emphasize the need for better diagnostic and intervention tools for children at-risk of developing dyslexia.

In the present article, we investigate current constraints of behavioral assessments of reading impairment in childhood and examine the potential of neuronal imaging as a diagnostic technique for the identification of biological markers in pre-literate children.

Challenges with Behavioral Approaches

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (APA, 2022) categorizes dyslexia as a specific learning disorder consisting of difficulties with word recognition, reading fluency, decoding, and/or spelling. Historically, dyslexia has been understood as an unexpected underachievement in word-level reading, meaning the difficulty is not attributable to an intellectual disability, cultural factors, disorders of sensory perception, or educational scarcity (Zumeta et al., 2014). Early research into dyslexia inferred a neurological origin, so any observable behavior that might be considered a sign of a neurological dysfunction (e.g., hyperactivity, sensory-motor difficulties) could form the basis for identifying dyslexia (Fletcher et al., 2018). The difficulty of supporting such inferences based on indirect behavioral measures and the lack of evidence in the use of sensory, perceptual, and motor interventions to improve academic outcomes led to the pursuit of other identification methods (Fletcher et al., 2018).

Much research has been devoted to approaches of cognitive discrepancy to conceptualize reading impairments and was the basis for identifying dyslexia in accordance with US federal regulations for decades (U.S. Office of Education [USOE], 1977). A well-known hypothesis in this category is the intelligence (IQ)-academic achievement gap, where one's full-scale IQ score should be statistically significantly above their achievement score to identify dyslexia (Rutter & Yule, 1975). There are many known psychometric problems with this approach (Fletcher et al., 2002), but one obvious weakness is the need to "wait to fail," meaning one just needs to stay in school long enough without progressing significantly in word-level reading in order to be identified with dyslexia, a process contradictory to early identification. Several studies have since questioned the validity of this method (Gresham & Vellutino, 2010; Stuebing et al., 2002) in addition to identifying problems with its implementation (Haight et al., 2001), thus resulting in this approach no longer being favored in diagnosing dyslexia.

Another cognitive discrepancy approach examines intra- and interindividual differences in cognitive or academic skills to detect a pattern of strengths and weaknesses (PSW) to characterize dyslexia (Miller et al., 2016). Within this approach, multiple methods have been proposed and

studied, but the methods typically include collecting data from multiple sources to identify a person's cognitive and academic strengths and weaknesses and evaluating the relationship between the functioning of different cognitive domains (e.g., working memory, phonological processing) to the person's academic weaknesses (Alfonso & Flanagan, 2018). The research examining the reliability and validity of a PSW approach to diagnosing dyslexia so far has been limited (Maki & Adams, 2020; Stuebing et al., 2012), in part, because of the multiple methods within this category.

Response to intervention (RTI) is a behavioral framework typically within a multi-tier system of support (MTSS) that assesses how a child performs following high-quality instruction and progressively intensive supports (Gersten et al., 2008). Prevention and early intervention are key principles of RTI, where reading difficulties are determined by peer comparison of achievement, and how a child responds to evidence-based instruction compared to peers can serve as a justification for a dyslexia diagnosis (Fletcher & Vaughn, 2009; VanDerHeyden et al., 2007). While RTI has been shown to be an effective process for identifying students who require extra support in reading and preventing some children from requiring special education services (Coyne et al., 2018; Vaughn et al., 2010), several issues with its implementation have been identified (Reynolds & Shaywitz, 2009), including potentially delaying an evaluation for dyslexia while tiered interventions and progress monitoring are enacted. RTI can be difficult to implement with fidelity since it requires school personnel to be highly knowledgeable in the use of comprehensive screeners and evidence-based interventions (Balu et al., 2015). In addition, an RTI framework has not yet shown to be a reliable and valid approach to identifying dyslexia (Hendricks & Fuchs, 2020). Due to the limitations highlighted with each of these methods, a consensus on dyslexia identification based on behavioral approaches has yet to be validated (National Association of School Psychologists [NASP], 2022).

Neuroscience of Reading Research

Neuronal activity in human subjects is commonly assessed using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) techniques. These imaging tools are regularly employed to identify fluctuations in electrical (EEG) and vascular changes (fMRI) associated with cognitive processes (Debener et al., 2006). Specifically, the detection of neuronal activity alterations across experimental conditions is used to identify the position and magnitude of neural circuits associated with cognitive tasks (Cichy & Oliva, 2020). The ability to use high temporal (EEG) and spatial (fMRI) resolution during experimental paradigms make these techniques excellent tools for the identification of

physiological correlates of reading processes (Carter et al., 2019; Duffy et al., 1980). It has been demonstrated that these tools can be useful in the evaluation of reading impairments (Gallego-Molina et al., 2022; Ortiz et al., 2020). Importantly, these studies have demonstrated that assessment of reading processes using neuro-imaging tools can lower the age of diagnosis for children with dyslexia (Chyl et al., 2021; Ortiz et al., 2020) and identify abnormal neural activation patterns prior to formal literacy instruction (Schivone et al., 2014; Wilkinson et al., 2020). The purported reduction in the age of diagnosis using physiological markers introduces the possibility of a foundational improvement in the effectiveness of reading intervention outcomes.

Event-Related Potential in Language and Reading Research

Event-related potential (ERP) procedures provide correlational information about neuronal activity and cognitive, motor, and/or sensory processes. Variations in voltage potential using scalp electrodes are time-locked to recurrent experimental conditions to identify temporal and spatial features of neural responses. Currently, several ERP components (N1/N170, P200 and N400) are well accepted as electrophysiological signatures of language information processing (Friederici et al., 1996; Penke et al., 1997; Perry, 2022). The use of ERP measures in reading research provides investigators information about discrepancies in neuronal activity between typically developing reading children and those diagnosed with dyslexia. This electrophysiological information can be used to edify behavioral observations in children suspected of being dyslexic. In particular, ERP measures offer three distinct advantages over behavioral diagnostic approaches. First, ERPs provide millisecond temporal resolution (Molfese et al., 1999). Second, ERPs are time-locked to experimental conditions making it possible to determine what stages of reading ability are impaired (Gao et al., 2022). Third, the relatively non-invasive qualities of ERPs combined with the capacity to conduct recordings in passive conditions allow investigators to measure neuronal activity in children of all ages. These technical advantages provide information that cannot be captured using traditional behavioral measures and may provide the ability to assess the likelihood of future reading impairments in pre-reading level children.

Functional Magnetic Resonance Imaging in Language and Reading Research

Functional magnetic resonance imaging identifies fluctuations in oxygenated-blood flow across cerebral structures. These changes in the blood-oxygen-level-dependent (BOLD) signal are used to indirectly determine the location

of neuronal networks activated during sensory, motor, or cognitive processes. Despite temporal limitations associated with the BOLD signal (seconds), the non-invasive features of fMRI have been employed to examine the loci of neuronal activation in typical and atypical readers (Barouch et al., 2022; Hoeft et al., 2007; Taran et al., 2022). Reports of reading research employing fMRI have been able to answer questions not easily addressed by behavioral or ERP techniques. In particular, fMRI can help identify cortical and sub-cortical brain regions associated with reading processes, dissociate differences between networks employed by children and adults, and distinguish the impact of writing systems on neuronal activation as experienced by bilingual individuals. For example, Cao et al., (2006) conducted an fMRI study where participants had to indicate whether word pairs with either similar phonology but different orthography (e.g., jazz-has) or similar orthography but different phonology (e.g., pint-mint) rhymed. They demonstrated that children and adolescents with dyslexia displayed hypoactivation in the left inferior frontal gyrus, left inferior parietal lobe, left inferior temporal gyrus/fusiform gyrus, and left middle temporal gyrus compared to a control group. This research codifies brain regions important to orthographic and phonological representations, their interrelated activation, and phonological processing.

Together, ERP and fMRI investigations can be used to produce a high temporal (ERP) and spatial (fMRI) map of the neuronal networks involved in reading processes. These maps can then be used to determine deviations between typical and atypical readers and provide physiological information about possible impairments in reading.

Neurophysiological Assessments of Reading Ability

It has been demonstrated that measures of neuronal discrimination of speech signals in childhood can be used to predict reading performance later in life (Molfese & Betz, 1988). The authors reported that infants capable of discriminating consonant sounds from combined consonant–vowel sounds, as assessed by ERP signals, developed effective language skills years later (Molfese & Molfese, 1997). Since then, several studies have established that neural responses to auditory stimuli in infancy can be predictive of later reading performance (Espy et al., 2004; Molfese, 2000; Molfese et al., 2001; Schivone et al., 2014). Furthermore, van Zuijen et al., (2013) demonstrated that measures of infant ERP among children at familial risk for dyslexia can be used to predict who will develop reading difficulties in the future. This research presents clear evidence of the utility of ERP as an early biomarker for dyslexia and the possibility for intervention at much younger ages.

Children with dyslexia show significant variation in neural response activation across multiple brain regions compared to their non-dyslexic peers. This can be seen in the brain stem, where children with dyslexia show greater variability in auditory brain stem responses to speech (Hornickel & Kraus, 2013; Liebig et al., 2020), and more broadly in the left hemisphere, where hypoactivation of temporoparietal and occipitotemporal networks is prevalent (Richlan, 2020; Shaywitz et al., 1998, 2002). These differences in neurophysiological responses occur in children diagnosed with dyslexia as well as emerging readers, indicating a risk for later reading difficulties (Espy et al., 2004; Molfese, 2000; Norton et al., 2015).

Recent investigations have expanded the analysis of acoustic processing to visual discrimination tasks (Premeti et al., 2022; Schulte-Korne & Bruder, 2010). These experiments have revealed that deviations in the ERP signal, about 200 ms after stimulus onset, correlate with visual-orthographic processing and occur over the left occipital-temporal cortex (Maurer & McCandliss, 2008; Michel et al., 2004; Rossion et al., 2002; Tarkiainen et al., 1999). The findings of this signal have been used to identify the emergence of literacy by measuring the variations in neuronal activity as a function of literacy training in children (Maurer et al., 2006; Romanovska et al., 2022). In addition to the analysis of auditory and visual processing, electrophysiological investigations have determined that ERP signals near 400 ms post stimulus correlate with semantic evaluation (Deacon et al., 2000; Gomes et al., 1997; Holcomb, 1988; Kutas & Hillyard, 1984; Morgan et al., 2020). Furthermore, fMRI studies have identified the location of neuronal networks involved in reading. In particular, it has been reported that a large-scale network of left frontal, temporoparietal, and occipitotemporal regions are activated during reading (Turkeltaub et al., 2003). For example, the left occipitotemporal cortex, known as the ‘visual word form area’ is activated by visual reading regardless of the writing system (Chen et al., 2019; Houde et al., 2010). Young children who go on to develop dyslexia, however, have been shown to display under-activation of the visual word form area when exposed to letters (Centanni et al., 2019).

Conclusions

Behavioral assessments of dyslexia have several limitations that can result in problems identifying dyslexia and delaying intervention. Furthermore, mixed results from research on the reliability and validity of different behavioral approaches has led to a lack of consensus on how to accurately diagnose dyslexia (NASP, 2022). ERP and fMRI studies show that neuronal activation in children can be used to identify reading disabilities and enhance behavioral measures (Myers et al.,

2014). Additionally, while behavioral methods cannot predict how children with dyslexia will respond to intervention, neuroimaging approaches have the potential to differentiate which individuals will benefit from behavioral interventions (Hoeft et al., 2011). These neuronal assessments may hold the key for the earlier identification of dyslexia and ultimately improve the outcome of reading interventions in children.

Neuronal Plasticity

The findings discussed in the present paper were mainly limited to human studies; however, it should be noted that the fundamental principles of neuronal networks have historically been identified in animal models (Merzenich et al., 1984). It is the invasive work of animal research that has furthered our understanding of the molecular and cellular properties that modulate neuronal networks and ultimately cognitive abilities (Lampis et al., 2021; Merzenich & Sameshima, 1993). Therefore, researchers as well as clinicians involved in human studies should be informed about the findings of neuronal plasticity studies that examine the settings (spatial and temporal) that optimize behavioral interventions. The well-researched idea of sensitive periods plays a fundamental role in the necessity of early identification of dyslexia and emphasizes the need to lower the age of diagnosis to improve behavioral outcomes (Knudsen, 2004).

Accessibility

Neuroimaging techniques have evidenced their utility in the early identification of dyslexia (Molfese & Betz, 1988; Shaywitz et al., 2002); however, the financial burden of using these methods to screen all pre-literate children has made the diagnostic utility of this approach impractical. However, developments in open-source software and hardware may hold the solution for the implementation of EEG assessments in school settings (Debener et al., 2012). The reduced cost and ease of access to EEG technology is paving the way to the possible introduction of EEG assessments to children regardless of geographical location or financial situation. Indeed, in comparison to a PSW approach, EEG has the potential to be more cost-effective (Williams & Miciak, 2018). Future research on implementation costs will be needed to further justify the use of EEG technology to screen children at risk of developing dyslexia.

Future Research

The use of neuroimaging techniques in the prediction of reading disabilities has been substantiated (Centanni et al., 2019; Hoeft et al., 2011). However, the copious lack of longitudinal studies and small sample sizes has limited the

support of these neuroimaging techniques as diagnostic tools for dyslexia. Future experiments will require longitudinal examinations that explore the usefulness of these techniques in clinical assessment settings with larger sample sizes than those reported up to now. Last, studies that employ neuroimaging as a tool of assessment should be conducted to measure the increase of diagnostic effectiveness, screening utility, and age of identification. These measures will help map the future role these techniques will have in the assessment of dyslexia and the timely treatment of this challenging disability that affects so many children.

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Declarations

Conflict of interests The authors declare no competing interests.

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