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Evidence of a posterior cingulate involvement (Brodmann area 31) in dyslexia: A study based on source localization algorithm of event-related potentials

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Abstract

The study investigates the differences regarding the position of intracranial generators of P50 component of ERPs in 38 dyslexic children aged 11.47±2.12 years compared with their 19 healthy siblings aged 12.21±2.25. The dipoles were extracted by solving the inverse electromagnetic problem according to the recursively applied and projected multiple signal classification (RAP-MUSIC) algorithm approach. For improved localization of the main dipole the solutions were optimized using genetic algorithms. The statistical analysis revealed differences regarding the position of intracranial generators of low frequency of P50. Particularly, dyslexics showed main activity being located at posterior cingulate cortex (Brodmann's area 31) while controls exhibited main activity being located at retrosplenial cortex (Brodmann's area 30). These results may indicate a role for the posterior cingulate cortex in the pre-attentive processing operation of dyslexia beyond of its traditional function in terms of spatial attention and motor intention.

Keywords: Dyslexia; Event-related potentials; Genetic algorithms; RAP-MUSIC; Source localization

1. Introduction

Attentional and working memory (WM) operations have been implicated in the pathophysiology of developmental disorders of scholastic skills or alternatively 'dyslexia'. (Montgomery, 2003; Toplak et al., 2003; Webster and Shevell, 2004). However, despite extensive research in the field, the nature of the core deficits in the patterns of cognitive characteristics of dyslexia has remained poorly understood and heavily debated (Fitch and Tallal, 2003; Vellutino et al., 2004; Shaywitz and Shaywitz, 2005).

A promising prospect within this field may be the use of long latency electroencephalogram (EEG) or endogenous evoked potentials (ERP), because of their association with cognitive constructs and processes (Fabiani et al., 2000). Recently, it has been shown that dyslectic children manifest abnormal aspects of pre-attentive processing of information as they are reflected by P50 elicited during a working memory test. (Papageorgiou et al., 2005). In particular dyslectic group showed prolonged P50 latency induced by the low tone, located at the frontal area. The amplitude of P50 induced by the low tone exhibited significantly negative associations both with age and memory performance, while age and memory performance were associated positively. These findings have been conceived as index that pre-attentive processing deficits may be implicated in dyslexia.

Abbreviations: ERPs, event-related potentials; RAP-MUSIC, recursively applied and projected multiple signal classification; BA, Brodmann area; WM, working memory.

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The distribution of the intracranial generators of P50 component can provide valuable information for the pathophysiological mechanisms of dyslexia. The determination of intracranial generators from EEG or ERP scalp recordings can be performed using two general approaches: dipole and imaging methods (Michel et al., 2004). Dipole methods assume that the electrical activity of the brain can be modeled by a small number of dipoles, while imaging methods are based on the assumption that the primary current sources are distributed in a 3D grid of solution points.

In previous studies related with source localization analysis of ERP scalp activity, it was assumed that there are discrete sources of neural activity that can sum linearly to form the scalp recordings (Makeig et al., 1996). In cases that are characterized by highly focal activation, dipole methods can be used to determine the sources of the neural activity with accuracy. Recursively applied and projected multiple signal classification algorithm (RAP-MUSIC) is a dipole method for the solution of the inverse electromagnetic problem (Mosher and Leahy, 1999). Simulations have shown that the RAP-MUSIC algorithm is a powerful method to determine dipole sources even in cases where the number of electrodes is small (15 sensors). The accuracy of dipole localization using the RAP-MUSIC algorithm has been also investigated in a later study using statistical analysis methods (Darvas et al., 2004).

Recently, a number of studies have been presented using the RAP-MUSIC method with real data. RAP-MUSIC algorithm has been used for the source analysis of interictal spikes from patients with epilepsy and hypothalamic hamartoma using EEG scalp recordings (Leal et al., 2002). According to the results of this study, the sources that produce all the spikes with good signal to noise ratio were found in the neighbourhood of the hamartoma, with late sources located in the cortex. Moreover, the RAP-MUSIC algorithm in combination with independent component analysis was efficiently used to estimate epileptic sources in real epileptiform EEG discharges (Kobayashi et al., 2002). This source localization approach estimated generally correct epileptic sources in 3 patients and its performance was superior to other localization methods. To our knowledge, no previous works on the application of RAP-MUSIC algorithm to source analysis of early components of ERP have been reported.

Taking into account the above considerations, the present study was designed to implement the RAP-MUSIC technique for determining the intracranial generators distribution associated with the P50 component of ERPs recorded in children with dyslexia. Based on the findings of previous research, the working hypothesis was that the evaluation of the brain activation of the associated P50 component elicited during a WM test using the RAP-MUSIC technique would allow the identification of neural circuits involved in the pathophysiology of pre-attentive operation in dyslexia. The main purpose of this work is to gain a better understanding of the possible psychophysiological mechanisms with regards to specific learning difficulties. The study focused on differences regarding the position of the main intracranial generators of P50 component of ERPs in dyslectic children compared with their healthy siblings.

2. Methods

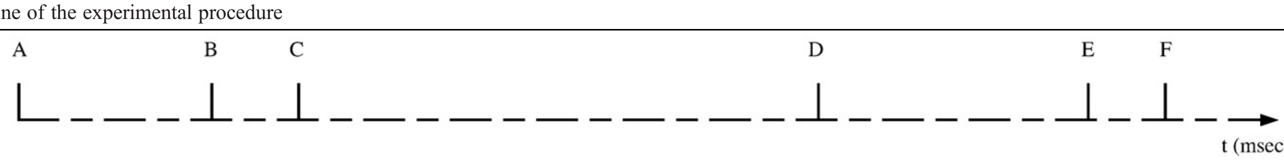
2.1. Stimuli and procedure

The subjects were evaluated with the digit span Wechsler Auditory test (Wechsler, 1955). For each trial of the experiment, rest EEG signal was recorded for 500 ms. A single sound tone of either high (3000 Hz) or low frequency (500 Hz) was presented to the subjects through earphones, followed by the numbers which had to be memorized. At the start of this tone, ERP signal was recorded for 1000 ms while the warning stimulus lasted 100 ms. At the end of the number sequence presentation, the same signal tone was repeated. If the frequency of the signal tone was low, the subjects had to recall the numbers in the same order with that presented, else (high frequency tone) the subjects had to recall the numbers in the reverse order. The total task consisted of 52 repetitions for a period of about 45 min. An outline of the procedure is provided in Table 1.

2.2. Subjects and procedures for data acquisition

Fifty seven (57) children participated in the study. Thirty eight (26 boys and 12 girls) of them were outpatient cases who had been diagnosed as having dyslexia according to the 10th

Table 1
Outline of the experimental procedure



Time period	Action
AB (500 ms)	Recording of EEGs.
BC (100 ms)	Warning stimulus (500 or 3000 Hz, 65 dB) and recording of ERPs.
BD (1000 ms)	Recording of ERPs.
DE (varies) (not in scale)	Computerized administration of the sequence of numbers of the Wechsler Direct Auditory Memory Test. The duration of this period depends on the numbers of digits to be recalled in each trial (from two to nine digits across trials). However, between each pair of administered digits, the time interval is 1 s.
EF (100 ms)	Repetition of the warning stimulus.

edition of the International Classification of Diseases (ICD-10) and the rest 19 children (7 boys and 12 girls) were healthy sibling of the dyslexic group. The mean ages for the dyslectic children and for the controls were 11.47±2.12 and 12.21±2.25 years, respectively. Participants did not enter the study if they had (1) clinically notable neurological disease (including seizure disorder), (2) a history of head injury, (3) hearing difficulties and (4) attention deficit disorder and hyperkinetic syndrome. For more information see (Papageorgiou et al., 2005).

Prior to participation in the examination, parents were informed about the aims of the study, received a full description of the procedure, and provided written consent. Children were tested individually. The investigators explained to each child the procedure and the children gave also their consent. The study was approved by the local ethical committee.

The children's EEG/ERP signals were recorded at 15 electrodes (Fp1, F3, C5, C3, Fp2, F4, C6, C4, O1, O2, P4, P3, Pz, Cz, Fz) according to the 10–20 international system, referred to both earlobes. The Ag/AgCl electrodes were attached to the scalp with adhesive cream in order to keep the electrode resistance below 5 kΩ. An electrode placed on the subject's forehead served as ground. The passband of the amplifiers was set from 0.05 Hz to 35 Hz. During the recordings, the subjects had their eyes closed in order to minimize eye movements and blinks. Eye movements were recorded through electro-oculogram (EOG) and recordings with EOG higher than 75 μV were rejected. All signals were sampled at frequency of 1 kHz so that for signals in the frequency range 0–35 Hz the Shannon theorem is over satisfied. Since noise (signals that are not EEG/ERP) is considered to be a random process with zero mean value, the EEG/ERP signal's SNR was improved by averaging across the 52 trials of the experiment.

2.3. Source localization

In this study, the recursively applied and projected multiple signal classification (RAP-MUSIC) algorithm was used to scan the head volume and to determine the position of the intracranial generators (Mosher and Leahy, 1999). The RAP-MUSIC method falls in the category of dipole or scanning methods and is an improvement of the original MUSIC method (Mosher et al., 1992). The basic idea of the MUSIC method is to separate the whole spatio-temporal data into the signal and noise subspaces. The whole head volume is then scanned in order to find those sources that contribute to the signal subspace. At each location in the head volume, the algorithm computes the forward model and projects it to the signal subspace to calculate the similarity (subspace correlation) between the modeled and original data. Locations that have high values of correlation indicate probable dipole locations.

In the RAP-MUSIC algorithm the scanning procedure runs iteratively. In the first iteration the dipole location that produces the maximum correlation is determined. In subsequent iterations the dimension of the signal subspace is reduced projecting away from the previous solutions. The iteration process is repeated until the remaining space achieves a correlation lower than a set threshold. This comprehensive scanning of the head volume ensures that the algorithm will not be trapped in a local minimum. The results of RAP-MUSIC algorithm consist of the dipole location and orientation as well as its activation curve. The algorithm allows the use of solutions other than single dipole but in this study only this option was used.

In scanning methods the main problem is that the number of sources must be defined a priori. The singular value decomposition (SVD) method is used to define the effective rank of the signal space that has lower dimension of the ERP data. In the present study the RAP-MUSIC algorithm was used with a 0.94 correlation threshold and a rank equal to 3. Using the specific values of the rank and correlation threshold, the RAP-MUSIC algorithm in most cases resulted in one dipole source. Taking into consideration the fact that the value of the correlation of the dipole source with the signal space is high (0.94), one main generator of the P50 component can be assumed. In order to determine a confidence ellipsoid area around the location of the dipole, the confidence intervals of the x, y and z coordinates of the strongest dipole location were estimated using the bootstrap method (Efron and Tibshirani, 1993).

For the RAP-MUSIC source localization method, the Brainstorm open source Matlab toolbox was used (Mosher et al., 2005). The specific toolbox provides tools for the resolution of the forward and inverse problems. In this study, a spherical three-shell head model representing brain, skull and scalp (radius ratio, scalp radius = 100.26 mm), was used for the resolution of the forward problem (Berg and Scherg, 1994). The conductivity of the three shells, brain, skull and scalp was $3.3\times10^{-4}/(\Omega\ \text{mm})$, $0.042\times10^{-4}/(\Omega\ \text{mm})$ and $3.3\times10^{-4}/(\Omega\ \text{mm})$ respectively.

2.4. Genetic algorithms

The iterative search of non-linear parameters (such as the main dipole of intracranial activity) using gradient or direct search methods is a generally accepted and broadly applied procedure. However, one of the drawbacks of these optimization methods is their sensitivity to the supplied initial parameters and their trapping to local optima. Such problems can be faced using genetic algorithms (GA) (Michalewicz, 1996). They have already applied to a wide range of biomedical applications. Artificial neural network models constructed by GAs have been successful in the challenging task of emotion recognition through cardiovascular features (Yannakakis et al., 2007). As regards EEG source localization there have been some attempts to improve source localization accuracy (McNay et al., 1996).

Genetic or evolutionary algorithms are a class of adaptive optimization techniques based on Darwinian principles of natural selection and survival of the fittest. In the initialization of the algorithm, some proposed solutions are randomly generated to form an initial population. The population size depends on the nature of the problem. The population is generated either randomly covering the entire range of possible solutions (the *search space*) or the solutions may be "seeded" in areas where optimal solutions are likely to be found.

During each successive generation, a proportion of the existing population is selected to breed a new generation. Individual

Table 2
Results of independent-samples tests controlling for group factor

Stimulus frequency	Group	x (mm)	y (mm)	z (mm)	Wider area
High	Controls	0.4	−17.5	34.2	Left cerebrum, limbic lobe, cingulate gyrus, gray matter, Brodmann area 24
	Dyslexics	−2.4	−10.7	37.2	Left cerebrum, limbic lobe, cingulate gyrus, gray matter, Brodmann area 24
Low	Controls	8.4	−52.5	16.2*	Right cerebrum, limbic lobe, posterior cingulate, gray matter, Brodmann area 30
	Dyslexics	7.8	−32.2	41.2*	Right cerebrum, limbic lobe, cingulate gyrus, gray matter, Brodmann area 31

Asterisk denotes statistically significant difference at the 0.05 level.

solutions are selected through an objective function, where fitter solutions are more likely to be selected. Most functions are stochastic (roulette wheel selection, tournament selection) and designed so that a small proportion of less fit solutions can be also selected in order to keep the diversity of the population large and to prevent premature convergence on poor solutions. Once the individual solutions have been selected, the genetic operators of crossover (also called recombination) and/or mutation take place. By producing a "child" solution using the above methods of crossover and mutation, a new solution is created which typically shares many of the characteristics of its "parents". New parents are selected for each child, and the process continues until a new population of solutions of appropriate size is generated. These processes ultimately result in the next generation population that is different from the initial generation. Generally the average fitness will have increased after some generations, since the best solutions from the first generation and selected solutions from next generations take part in the procedure and survive.

The motivation for choosing a GA for finding the location of the main dipole source is that the Nelder–Mead simplex method (Lagarias et al., 1998) (the minimization method that RAP-MUSIC applies) is susceptible to trapping in local optima and strong dependency on initial estimates. These can be overcome by using GA and even better by using the combination of GA and simplex method as a hybrid system where the simplex method is applied to each successive GA population. In a recent work (Maeder et al., 2004), GAs were compared with the Nelder–Mead simplex method (Lagarias et al., 1998) (the minimization method that RAP-MUSIC applies) revealing the advantages of GAs to approach a solution near a global optimum in solution space with many local optima, such as the locations of intracranial dipoles that best solve the forward problem. Also a hybrid GA–simplex method appears with better accuracy than conventional GA approach (Zhou et al., 2004). In this work, the population size of the used GA consisted of 20 (x, y, z) Talairach coordinates (Talairach and Tournoux, 1988), the algorithm ran for 200 generations and the probabilities of crossover and mutation were 0.2 and 0.6, respectively. The initial population was determined by the better 20 (x, y, z) Talairach coordinates produced by simplex method.

2.5. EEG–MRI registration

To define the dipole positions within the structural MRI, a co-registration between the EEG space and the MRI space was performed. The registration procedure involved the use of a transformation (rotation and scaling) that was done using the nasion and pre-auricular points as fiducial points. The registration was performed using a single template MRI from the Montreal Neurological Institute (Collins et al., 1998).

3. Results

3.1. Statistical analysis of source positions

The dependent variables used for the analysis were the x, y and z Talairach position coordinates values of the main source extracted using the RAP-MUSIC method. The independent qualitative factor was the subjects' group (healthy, dyslexia). Data were checked through Kolmogorov–Smirnov test for their normality. Two multivariate linear analyses were applied, one for the high and the other for the low frequency tone. Also, using independent sample t-tests, it was examined for which variables the two groups differed significantly between each other. Statistical significance was set at the 0.05 level.

3.2. Source location comparisons

The independent samples t-test procedure revealed a significant effect of the group factor on the z Talairach position coordinate of the main source under the low frequency stimulus ($t(55)=2.66$, $p<0.05$). The results are presented in Table 2.

It appears that in dyslexics the main source is located in subcortical areas (Limbic Lobe, Cingulate Gyrus, Gray Matter, Brodmann area 31) whereas in controls it is located in cortical areas (Limbic Lobe, Posterior Cingulate Gyrus, Gray Matter, Brodmann area 30), as shown in Fig. 1.

The sagittal plane corresponds to the y–z coordinates plane and it is selected to be presented for better visualization.

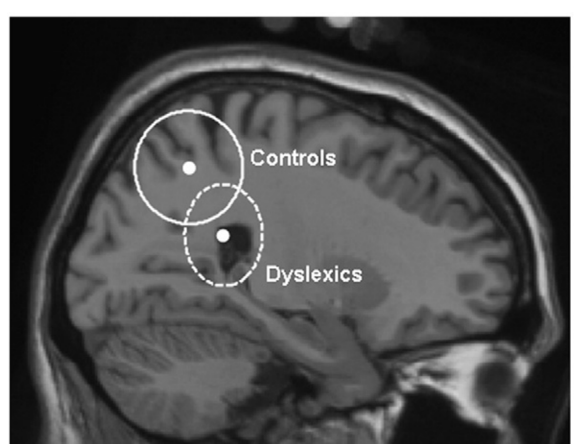


Fig. 1. Confidence ellipsoid area (CI) for the coordinates of the main dipole location (P50 low frequency) for controls and dyslexics. The source location was projected at the sagittal plane.

4. Discussion

Based on the findings of previous research, the current working hypothesis was that the evaluation of the brain activation of the associated P50 component elicited during a WM test using the RAP-MUSIC technique (Mosher and Leahy, 1999) would allow the identification of neural circuits involved in the pathophysiology of dyslexia. Hence, this study investigated the differences of the distribution of intracranial generators associated with the auditory P50 component of ERPs elicited during a WM test in children with dyslexia as compared to their healthy siblings. This approach revealed that the exposure to the low frequency tone was associated with a difference in the distribution of the P50 generators at certain brain networks, with regard to the groups in comparison. Particularly, in dyslexics the main source was located at right cerebrum, limbic lobe, cingulate gyrus, gray matter (Brodmann's area 31) whereas in controls the main source was located at right cerebrum, limbic lobe, posterior cingulated, gray matter (Brodmann's area 30).

The obtained results appear to be in agreement with those reported by Temple et al. (2003), who using fMRI technique revealed posterior cingulate activations in children with dyslexia after remediation. Remediation resulted in improved language, reading performance, and increased activation in multiple brain regions including posterior cingulate cortex, during phonological processing. In line with this a study of the brain correlates of language perception and auditory attention in adult dyslexics using fMRI methodology, reported that the posterior cingulate cortex showed activation for acoustic changes in the well-compensated dyslexic subjects who participated in the study (Ruff et al., 2003). This finding has been conceived as an index of developed compensatory cognitive strategies to alleviate basic dysfunctions such as lack of automatism in speech and written language processing. In this sense the posterior cingulate has been proposed 'as a possible candidate for this compensation'. Taking into account these observations in conjunction with the notion that the P50 component of ERPs is an index of pre-attentive processing (Clementz et al., 1997; Zouridakis et al., 1997), it is reasonable to assume that the findings of the current study suggest that the posterior cingulate cortex plays a key role in the pre-attentive processing operation of dyslexia beyond of its traditional function in terms of spatial attention and motor intention (Shannon and Buckner, 2004).

The fact that in the present study differences between the two groups were observed only after exposure to the low frequency but not to the high frequency warning stimuli supports the claim that perceptual deficits of children with dyslexia occur only in particular sound context (Wright et al., 1997; Sutter et al., 2000; Nelken, 2004; Petkov et al., 2005). This is in agreement with the finding that groups of adult and child dyslexics performed significantly worse than matched controls at discriminating frequency changes of sounds (McAnally and Stein, 1996; Witton et al., 1998).

Considering RAP-MUSIC, its application in the present study appears to provide some aid towards the understanding of the underlying mechanisms of dyslexics regarding the part of brain information processing which corresponds to the pre-attentive operation. Being employed effectively in the determination of epileptic sources from real epileptic EEG discharges (Kobayashi et al., 2002; Leal et al., 2002), RAP-MUSIC promises to shed light in the brain networks involved in manifestations of dyslexia. It would be argued that this could be reached taking into account the properties of this method which is able to detect and reveal the underlying sources with a high focal manner (Makeig et al., 1996). Furthermore, the introduced GA-based search for the localization of the main dipole results in more robust and reliable solutions.

However, caution is needed with regard to the generalization of the obtained results, which to some extent can be influenced by (a) the number of used EEG channels that could to some degree influence the spatial resolution (Gevins, 1998; Laarne et al., 2000) and (b) the use of a spherical three layer head model instead of a realistic one (Michel et al., 2004).

5. Conclusions

In conclusion, this study used the RAP-MUSIC method to examine the distribution of intracranial generators associated with the P50 component of ERPs in children with dyslexia as compared to their healthy siblings. The results may be indicative that the posterior cingulate cortex plays a key role in the pre-attentive processing operation of dyslexia beyond of its traditional function in terms of spatial attention and motor intention. While longitudinal studies that address pre-attentive issues in conjunction with working memory operation may provide useful information about the importance and causality of particular brain functions and behaviours in dyslexia, the current findings may offer an alternative interpretation of activation patterns in paediatric neuroimaging studies and encourage new hypotheses related to the aetiology of neurodevelopmental disorders. Furthermore, the obtained findings are supportive of the notion that the RAP-MUSIC method may provide insights in understanding the neurobiological framework implicated in dyslexia.

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