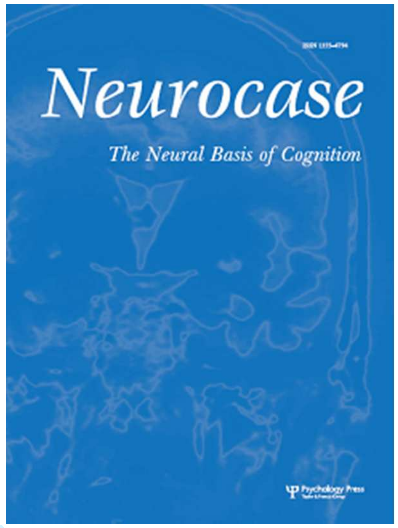


To read or not to read: a neurophysiological study

Journal:	*Neurocase*
Manuscript ID:	NCS-OA 13-207.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Mares, Ines; Instituto de Medicina Molecular(IMM), Faculty of Medicine, University of Lisbon, Language Research Laboratory Custodio, Pedro; Faculty of Sciences of the University of Lisbon, LASIGE Fonseca, Jose; Instituto de Medicina Molecular(IMM), Faculty of Medicine, University of Lisbon, Language Research Laboratory Bentes, Carla; Hospital Sta Maria Centro Hospitalar Lisboa Norte, EEG Laboratory Guerreiro, Manuela; Instituto de Medicina Molecular(IMM), Faculty of Medicine, University of Lisbon, Language Research Laboratory Guimarães, Nuno; Faculty of Sciences of the University of Lisbon, LASIGE; ISCTE-University Institute of Lisbon, Martins, Isabel; Instituto de Medicina Molecular (IMM), Faculty of Medicine, University of Lisbon, Dept Neurology
Keywords:	Alexia, Posterior cortical atrophy, ERPs, Reading, Progressive alexia

To read or not to read: a neurophysiological study

Running head (max 40 spaces): **ERPs correlates of pure alexia**

Inês Mares [1], Pedro Custodio [3], José Fonseca [1], Carla Bentes [2], Manuela Guerreiro[1],

Nuno Guimarães [3,4], Isabel Pavão Martins[1]

[1] Language Research Laboratory, Institute of Molecular Medicine (IMM), Faculty of Medicine University of Lisbon (FMUL)

[2]EEG Laboratory, Hospital Sta Maria Centro Hospitalar Lisboa Norte [3], Lisbon Portugal

[3] LASIGE, Faculty of Sciences of the University of Lisbon

[4] ISCTE-University Institute of Lisbon

Corresponding author: I. Pavão Martins, MD PhD; Language Research Laboratory, Department of Neurosciences, Lisbon Faculty of Medicine and Instituto de Medicina Molecular University of Lisbon, Lisboa, Portugal; Telephone/Fax: 351 217 934 480; E-mail: Isabel_Martins@fm.ul.pt

Abstract

Pure alexia (PA) has been associated with visual deficits or a failure to activate the visual word forma area (VWFA). We report a patient with alexia due to posterior cortical atrophy, in whom ERPs revealed a delay in the P100 component and an absent N170 compared with controls. Furthermore there was a tendency for a larger delay in P100 latencies associated with incorrectly read words. This suggests that some cases of PA might result from deficits in visual perception, signaled by the P100 early potential which could lead to an inability to consistently activate the VWFA, marked by the absent N170.

Key words: Alexia, letter-by-letter reading, Posterior cortical atrophy; ERPs

Introduction

Pure alexia, initially described by Dejerine (1982), is characterized by a selective reading impairment in the absence of spoken language or writing deficits. The typical underlying neuroanatomical lesion is localized in the left inferior temporo-occipital region, particularly in the left fusiform gyrus, or in the connection between that area and the primary visual cortex (Damasio & Damasio, 1983; Dehaene & Cohen, 2011). The severity of this syndrome is variable and some patients retain the ability to read individual words using a strategy called “Letter by letter reading” (LBL), whereby there is an abnormal latency to word production that increases with word length (Behrmann, Plaut, & Nelson, 1998). It has been argued that this behavior might be due to visual impairments (Starrfelt, Habekost, & Leff, 2009). In fact, these patients frequently display concomitant visual deficits and particularly a right hemianopia. Nonetheless, eye-tracking data reveals that patients with pure alexia have increased fixation frequency and longer word reading time in comparison with hemianopic dyslexia patients or virtual hemianopia subjects (Pflugshaupt et al., 2009). Furthermore, differences in damaged areas between those patients seem to indicate the involvement of the visual word form area (VWFA) on pure alexia but not in hemianopic dyslexia (Pflugshaupt, et al., 2009). This area has a selective response to word-like stimuli compared to visual non-orthographic stimuli such as line drawings (Szwed et al., 2011). VWFA has thus been proposed to support visual expertise for printed words allowing their fast and parallel processing (for a review see Dehaene & Cohen, 2011). Studies using both fMRI and ERP (Event Related Potentials) (Brem et al., 2006) or using ERP source analysis (Brem et al., 2006; 2009; Maurer, Brem, Bucher & Brandeis, 2005) have associated the neural activity of the VWFA to the N170 component of the visual evoked response. Likewise, as in fMRI studies, ERP data has consistently shown an increased N170 amplitude in response to word-like stimuli compared to visual non-orthographic stimuli such as symbol strings (Maurer et al., 2005). Thus, following the presentation of familiar words both VWFA activation and the N170 component should occur and the absence of the N170 component could indicate an impairment of fast or automatic reading.

We report a patient with a posterior cortical atrophy and a progressive reading difficulty, in whom reading was associated with LBL and with delayed and atypical ERPs, particularly for words that she could not read aloud. This case illustrates the potential interest of this technique to the evaluation, diagnosis and characterization of patients with primary reading impairments. It also suggests that the delays in the early visual potentials could lead to a lack of N170 even in correctly read words, further indicating that the residual ability to read in such cases results from the activation of alternative pathways other than through the visual word form area.

Case report

A 64-year-old, right handed retired female (AP) of Portuguese nationality was evaluated because of a progressive reading impairment beginning 2.5 years before. She had 17 years of formal education and her first language was Portuguese being also fluent in English, French and German due to her academic and professional activity as a translator. She first noticed an increasing difficulty in following television or film subtitles as if they were running too fast. Later on, as her reading ability progressively declined, she became unable to read books or even small daily news, due to her effortful and slow performance. She recognized that her memory was not as good as before, but otherwise there were no other complaints, namely of oral language, writing or on daily activities. An ophthalmologic evaluation showed a corrected visual acuity of 7/10 in the right eye, 10/10 in the left eye and a minor loss of the right inferior peripheral visual field sparing the macula. Her past medical history was unremarkable except for frequent migraine attacks with visual aura, for which she had twenty years previously a CT scan performed with no abnormal findings.

On examination, she showed a fluent speech with a rich vocabulary and an accurate insight to her puzzling reading difficulty, in which she could recognize words as such but had difficulty processing them. The neurological examination was otherwise normal.

A cognitive assessment (Garcia, 1984; Wechsler, 1997, De Renzi and Vignolo, 1962) revealed a marked visuo-spatial impairment. AP presented a normal performance in tests of spoken language (object naming, object identification by name, sentence comprehension, word repetition, syntactic comprehension in the Token test), immediate and working memory (digit span forward and backward), verbal abstraction (proverb interpretation) and writing to dictation or spontaneously. Nonetheless, she had a low age and education adjusted performance on verbal and nonverbal memory tests (logic memory, word pair associates and visual reproduction of the Wechsler Memory Scale) (Garcia, 1984; Wechsler, 1997) and on verbal fluency tests (at the level of - 2 standard deviations). Furthermore, she presented severe difficulties in shape and size discrimination and space and form perception (CORVIST and VOSP tests, (Warrington & James, 1991), could not perform the Line Orientation Test (Warrington & James, 1991), presented simultaneo-agnosia during the copy of drawings, had a mild impairment in a test of face recognition (Benton, Hamsher, Varney, & Spreen, 1983), and difficulty recognizing famous faces (20% correct)(Martins, Loureiro, Rodrigues, Dias, & Slade, 2010), although there were no reports of prosopagnosia in her daily life. She had a normal score in hue discrimination, could name 80% of colors and identify 100% of colors by name (Table 1 for the visuo-spatial examination). Even though she could easily write numbers and perform mental calculations, she could only name 56% of Arabic numbers and could not read roman numbers, which she did before.

Insert Table 1 here

AP could easily write letters and words to dictation, copy letters, match capital letters and match printed with handwritten letters without errors. She was also easily capable of spelling out words and reconstructing words orally from dictated letters, excluding a central reading disorder.

She could read aloud and identify single letters in multiple choice, but presented a word length effect with a worse performance as the number of letters increased. She read 100% of single letters, 68% on ≤3 letter words, 59% on 4-5 letter words and 30% on >5 letters words (see Table 1

for reading examination). Her reading performance was compared between English, French and and her native Portuguese language with a new set of 15 stimuli in each language matched for word length. She read correctly 26.6% French words but produced 33% French paralexias (riviére-revanche; chaise- chasse; poulet- pauvre) and read correctly 40% English words producing 33% English morphologic paraphasias (nose - mouse; car - can, foot - photo). In Portuguese, she correctly read 26.6% of the 15 words and produced 73% Portuguese paralexias, of which 63.6% were semantic (nariz (nose) – mês (month); carro (car) – campo (field); fato (suit) – tecto (ceiling)) and 36.4% phonological (pão (bread)– rão; copo (glass) – compe; café (coffee) – cavés).

A brain MRI (Figure 1a) demonstrated an atrophy of the posterior regions of both hemispheres with a dilation of the occipital horns of the lateral ventricles and an F-FDG Pet scan showed a bilateral occipital and temporal hypo metabolism more marked on the left hemisphere (Figure 1b SUP).

Insert Figure 1a here

A 72 channel EEG (international 10/20 electrode placement system) was performed using a Nihon-Kohden system (Neurofax - EEG 1200). Electroencephalographic background activity showed a dominant alpha rhythm with superimposed irregular and low amplitude theta bursts over the left temporal regions. In several recording periods, an asymmetry (higher than 50%) of the posterior alpha activity was documented suggesting a left posterior dysfunction. Furthermore, in the power spectrum analysis, there was a right posterior quadrant dominance of fast (alfa/beta) activities and a higher power of the slow (theta/delta) frequencies in the left posterior temporal regions (Figure 1cSUP).

Experimental reading tasks and ERPs (Event Related Potentials) evaluation

EEG was recorded while AP performed a single word reading task controlled for word frequency, grammatical class and word length. ERPs waveforms were compared to a control group of 15 participants (9 males and 6 females), with ages ranging from 23 to 35 years (M = 27.75 years) and no language disorders. Written informed consent was given by all participants. The consent form was read to the patient by her husband.

Stimuli consisted of a list with 129 words, divided in three classes (43 words each): function words, concrete content words and abstract content words (Marques, Fonseca, Morais, & Pinto, 2007). All classes were matched by word frequency (M=924.91±923.95 frequency in a 16.210.438 word corpus; Bacelar do Nascimento, 2001), and word length (M=6.07±1.70 letters). Word class did not differ in frequency ($F(3,168)=.13$, $p=.94$) nor word length ($F(3,168)=.47$, $p=.71$). Given time constraints, 189 trials were presented randomly chosen from the above list, with each word being displayed at least once and no more than twice (60 repeated words).

Individual words were displayed centrally during one second in which the patient was instructed not to read aloud. After that a red dot appeared, while the word remained on screen, indicating that the patient should try to read the word aloud. The word and the red dot remained on screen until response for a maximum of 10 seconds, with an inter stimulus interval of 500 ms.

All participants did the same procedure varying only the number of trials drawn in the same manner from the initial list (due to technical issues 8 participants performed 129 trials and 7 only did 60 trials).

ERP recording and analysis.

Brain electrical activity was obtained with the same EEG system described above, online referenced to the mastoids at a sampling rate of 1000 Hz. Impedances were kept below 10 kΩ. Data was afterwards downsampled to 256 Hz and re-referenced to the average of all electrodes. Data was band-pass filtered at 0.1-30Hz. Continuous data was epoched between -100 and 600 ms relative to

the onset of word display, using the -100 ms previous to word onset as baseline. Artifacts were automatically rejected using EEGLAB (Delorme & Makeig, 2004). Twenty-seven percent of trials were rejected for AP. An average of 7.5% of trials was rejected for controls. When comparing correctly and incorrectly read words on AP, 78 and 111 trials were included for each category respectively. After trial rejection 57 trials were kept for correctly read words, and 81 for words not read. Analysis of the P100 and N170 potentials focused on posterior occipital electrodes (Figure 2). Maximum amplitude for these two components was found on PO7 and PO8, and this electrode pair was selected for further analysis.Insert Figure 2 here

---

Mean latency of the P100 was obtained, for controls, at a time window ranging from98.56 to 158.56 ms. This range corresponded to - 20/+40 ms around the maximum amplitude of the P100 component on the grand averaged ERP. Since in AP the P100 was more dispersed, peak latency was determined in her case as the maximum peak between 117 ms and 254 ms.

These measures were then subjected to statistical analysis with a t-test modified for comparing single cases with relatively small samples (Crawford & Porter, 2002), used here to compare patient's latency of P100 on word reading with the control group. To compare correct and incorrect trials in AP, a bootstrap single-subject analysis was used. The difference between peak latencies in the above time window was used as the correct and incorrect contrast. This technique creates a large number of resampled datasets with the same number of trials per condition as before. For this, each trial is taken in a random and independent way, with replacement, from the original dataset. Differences between correct and incorrect peak latencies where calculated from 50 000 resampled datasets. Results were considered significant if the 5th percentile of the differences distribution was above 0, meaning at p>.05 (one-tailed).

Results

Behavioral results

AP had 41% accuracy in 189 words while all other participants had 100% accuracy (Figure 2). Accuracy did not depend of word type (function words, verbs, abstract and concrete words; $F(2,186)=1.176$, $p=.311$) nor word frequency divided in three groups (<1000 frequency in lexical corpus, 1001-2000, >2001; $\chi2$ (2) = 1.46, *p* = .482), but the typical word length effect was shown between 3 word length groups (3-4 letters, 5-6 letters, 7-11 letters; $\chi2$ (2) = 9.18, *p* = .01).

Insert Figure 3 here

Event related potentials

Compared to controls, the patient had delayed and less clear ERPs in response to single word presentation (Figure 4). Furthermore there was a significant difference in the latency of the first evoked response latency (P100) between patient and controls on both occipital electrodes PO7 ($t(14) = 7.76$, $p<.001$) and PO8 ($t(14) = 3.05$, $p=.009$). After the first initial component, there was a negative component (N170) in the controls' ERPs that is not clearly present on the patient's ERPs.

Insert Figure 4 here

Comparing the waveforms on AP between correct and incorrectly read words, the P100 component seemed to divide in an earlier and later component respectively (Figure 5), with a tendency for a faster waveform in association with words the patient could read. This difference did not reach statistical significance in PO8 although there was a non-significant trend in PO7 (p=.08). No amplitude differences were found. Responses to words correctly read by AP were also compared with those of 7 participants that had a similar number of trials (<60) on the PO7 electrode. In this

comparison, P100 peak on correctly read words in AP (126.9 ms) did not show a significant delay compared with controls (t(6) = 2.0, p=.09). Nonetheless incorrectly read words in AP showed a later P100 peak (208.3 ms) when compared with controls (t(6) = 10.8, p<.001).

Insert Figure 5 here

Discussion

We report the case of a 64 year old woman with a pure alexia due to a posterior cortical atrophy who presented abnormal electrophysiological response to words and in whom P100 showed a delayed P100 peak compared to controls,. To our knowledge the current study is the first to report ERP correlates in pure alexia due to posterior cortical atrophy. Furthermore it is the second ERP studies of pure alexia, after Neville, Snyder, Knight and Galambos (1979) who reported three patients with alexia and their ERP correlates.

AP presented with an insidious steady and progressive difficulty in reading, associated with marked visuo-perceptive and visuo-spatial impairments, in the absence of a primary ophthalmologic disorder, an intact insight of her situation, an MRI documenting posterior cortical atrophy and a bilateral occipito-temporal hypometabolism, more marked on the left hemisphere. These features are in accordance with the proposed diagnostic criteria for posterior cortical atrophy (Kas et al., 2011; McMonagle, Deering, Berliner, & Kertesz, 2006; Mendez, Ghajarania, & Perryman, 2002; Tang-Wai et al., 2004), with a predominance of ventral visual dysfunction. Cognitive assessment also disclosed a minor anterograde episodic memory defect and a low verbal fluency as is usual in posterior cortical atrophy (Kas, et al., 2011).

AP reading performance was consistent with a peripheral alexia, since she could spell out words and reconstruct words from dictated letters. She also presented a word length effect that is

usual in pure alexia. The bilateral dysfunction of the ventral occipital temporal cortex does not allow the identification of a circumscribed area responsible for reading impairment. Yet the preservation of written and spoken language, the lack of a word class or regularity effect, the ability to read letters and the word length effect suggest that the disorder is at the level of word form recognition. This could result either from a disorder of the VWFA itself or from a failure of its activation. Interestingly she had some word form information about incorrectly read words producing paraphasic errors within the stimuli specific language.

ERPs obtained during reading showed a delayed cortical response to printed words, involving the first cortical components, which suggests a primary cortical visual disturbance. This is in accordance with what is known about the pathology of posterior cortical atrophy, with typical visual deficits. AP had a delayed P100 and an absent N170. The current results differ from Neville, Snyder, Knight and Galambos (1979) who report for patients with alexia, alterations mostly at the N170 component sparing the P100. This data was collected at posterior sites (P3 and P4) from three patients with different etiologies but not posterior cortical atrophy. The differences found might suggest that different etiologies, and particularly posterior cortical atrophy, might have different underlying deficits as supported by ERP correlates.

In addition, ERPs in AP suggest an increased latency and wave disorganization in response to the stimuli that the patient could not read aloud, but a more typical response to the words the patient could read aloud not differing in P100 latency when compared with controls. Nonetheless due to the reduced number of trials no significant differences could be found between read and not read words in AP.

The known N170, associated with word reading and VWFA activation was absent confirming an early impairment of word processing. The lack of this component might be a further suggestion of its importance in the clinical symptoms of pure alexia. It could also suggest that this patient was

using alternative pathways to read, such as an orthographic phonologic conversion, but the lack of a regularity effect and a word length effect do not support this hypothesis.

These results document a neurophysiological correlate of visual dysfunction in posterior cortical atrophy. The pathophysiology of peripheral alexias in posterior cortical atrophy is controversial. While some authors attribute reading difficulties to the primary visual impairment leading to an inability to activate the cascade serial visual processing, others showed that reading can be dissociated from visual disturbances and might have no causal relation with it (Yong, Warren, Warrington, & Crutch, 2013).

We acknowledge some limitations to this study. Data from a single case study is difficult to generalize, especially since the use of ERP methodology usually relies on the grand-average of waveforms across participants. However, posterior cortical atrophy is an unusual form of presentation of degenerative brain disorders and rarely presents with a pure alexia but rather with dorsal stream disorders, like optic ataxia and Balint syndrome. In addition, it was not possible to obtain a large number of trials due to the patient inability to sustain long sessions of reading tasks. The latter contributes to waveforms with more noise in AP when compared with controls' grand average. Nonetheless, even in participants' individual data with less trials and more noise, it was still possible to identify an earlier P100 and a normal N170, suggesting that differences in AP can't be attributed just to these limitations.

This case shows that, in posterior cortical atrophy, the pattern of response to printed material is variable suggesting that an early and fast activation of the primary cortical areas, as demonstrated by a normal latency in P100, can lead to a more effective activation of the visual word form area leading to an accurate response. It also suggests that in early posterior cortical atrophy the response of the occipito temporal cortex might be crucial for correct reading. Although there are no clear results regarding the difference between correct and incorrectly read words, when

compared with controls the data suggests that a fast perception might facilitate the activation of a possibly dysfunctional visual word form area.

Although this report has the limitations of a single case study it suggests the visual cortical ERP might be useful in the diagnosis of peripheral alexias and might contribute to document the pattern of impairment in patients with inconsistent responses or without documented brain lesions in imaging.

Acknowledgments

This study was supported by a grant from Fundação para a Ciência e Tecnologia Portugal. RAPS. Reading Analysis with neuroPhysiological Signs, FCT. Coordinator: N. Guimarães. PTDC/EIA-EIA/113660/2009.

References

Bacelar do Nascimento, M. F. (2001). Um novo léxico de frequências do português *Homenagem ao Professor Herculano de Carvalho* (pp. prelo).

Behrmann, M., Plaut, D. C., & Nelson, J. (1998). A literature review and new data supporting an interactive account of letter-by-letter reading. *Cognitive Neuropsychology, 15*, 7-51.

Benton, A., Hamsher, K., Varney, N., & Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual*. New York, USA: Oxford University Press.

Brem,S., Bucher, K., Halder, P., Summers, P., Dietrich, T., Martin, E., & Brandeis. D. (2006). Evidence for developmental changes in the visual word processing network beyond adolescence. *NeuroImage,29*(3). 822-837. doi:10.1016/j.neuroimage.2005.09.023

Brem, S., Halder, P., Bucher, K., Summers, P., Martin, E., & Brandeis, D. (2009). Tuning of the visual word processing system: distinct developmental ERP and fMRI effects. *Human brain mapping, 30*, 1833-1844. doi: 10.1002/hbm.20751

Crawford, J. R., Garthwaite, P. H., & Porter, S. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia, 40*, 1196-1208.

Damasio, A. R., & Damasio, H. (1983). The anatomic basis of pure alexia. *Neurology, 33*(12), 1573-1583.

De Renzi, A., & Vignolo, L. A. (1962). Token test: A sensitive test to detect receptive disturbances in aphasics. *Brain, 85,* 665–678.

Dehaene, S., & Cohen, L. (2011). The unique role of the visual word form area in reading. *Trends in cognitive sciences, 15*, 254-262. doi: 10.1016/j.tics.2011.04.003

Dejerine J. (1892). Contribution à l'étude anatomo-pathologique et clinique des différentes variétés de cécité verbale. *Mémoires de la Société de Biologie*; *4*, *61*–90.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods, 134*(1), 9-21. doi: 10.1016/j.jneumeth.2003.10.009

Garcia, C. (1984). *A doença de Alzheimer. Problemas de diagnóstico clínico.* Tese de Doutoramento, Faculdade de Medicina da Universidade de Lisboa, Lisboa.

Kas, A., de Souza, L. C., Samri, D., Bartolomeo, P., Lacomblez, L., Kalafat, M., . . . Sarazin, M. (2011). Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain, 134*(Pt 5), 1464-1478. doi: 10.1093/brain/awr055

Marques, J. F., Fonseca, F. L., Morais, a. S., & Pinto, I. a. (2007). Estimated age of acquisition norms for 834 Portuguese nouns and their relation with other psycholinguistic variables. *Behavior research methods, 39*, 439-444.

Martins, I. P., Loureiro, C., Rodrigues, S., Dias, B., & Slade, P. (2010). Factors affecting the retrieval of famous names. *Neurological sciences, 31*, 269-276. doi: 10.1007/s10072-009-0176-x

Maurer U, Brem S, Bucher K, Brandeis D. (2005). Emerging neurophysiological specialization for letter strings. *Journal of Cognitive Neuroscience*,*17(*10):1532–1552.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. Trends in C*ognitive Sciences, 7*, 293-299. doi: 10.1016/S1364-6613(03)00134-7

McMonagle, P., Deering, F., Berliner, Y., & Kertesz, A. (2006). The cognitive profile of posterior cortical atrophy. *Neurology, 66*(3), 331-338. doi: 10.1212/01.wnl.0000196477.78548.db

Mendez, M. F., Ghajarania, M., & Perryman, K. M. (2002). Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. *Dement Geriatr Cogn Disord, 14*(1), 33-40. doi: 58331

Neville, H., Snyder, E., Knight, R., & Galambos, R. (1979). Event-related potentials in language and non-language tasks in patients with alexia without agraphia. In Lehmann & Callaway (Eds.), *Human evoked potentials* (pp. 269-283). New York: Plenum Press.

Pflugshaupt, T., Gutbrod, K., Wurtz, P., von Wartburg, R., Nyffeler, T., de Haan, B., . . . Mueri, R. M. (2009). About the role of visual field defects in pure alexia. *Brain, 132*(7), 1907-1917. doi: 10.1093/brain/awp141

Starrfelt, R., Habekost, T., & Leff, A. P. (2009). Too little, too late: reduced visual span and speed characterize pure alexia. *Cerebral cortex (New York, N.Y. : 1991), 19*, 2880-2890. doi: 10.1093/cercor/bhp059

Szwed M, Dehaene S, Kleinschmidt A, Eger E, Valabregue R, et al. (2011). Specialization for written words over objects in the visual cortex. *Neuroimage, 56*, 330–344. doi: 10.1016/j.neuroimage.2011.01.073.

Tang-Wai, D. F., Graff-Radford, N. R., Boeve, B. F., Dickson, D. W., Parisi, J. E., Crook, R., . . . Petersen, R. C. (2004). Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology, 63*(7), 1168-1174.

Warrington, E. K., & James, M. (1991). *The visual object and space perception battery.* Bury St. Edmunds: Thames Valley Test Company.

Wechsler, D. (1997). *Wechsler Memory Scale-Third Edition (WMS-III)*. San Antonio, TX: The Psychological Corporation.

Yong, K. X., Warren, J. D., Warrington, E. K., & Crutch, S. J. (2013). Intact reading in patients with profound early visual dysfunction. *Cortex*. doi: 10.1016/j.cortex.2013.01.009

Table 1. Visuo spatial and reading evaluation.

Visuo spatial examination		Reading examination		
Tests	Score/Max 19-07-2013 (5% cut-off)	Tests	11/10/12 Score/Max	07/05/13 Score/Max
Benton facial recognition	36/54	Arabic Numbers	10/18	6/18
Naming famous faces	15/74	Roman numbers	0/5	1/5
Object visual Naming	14/16	Letters	12/12 100%	11/12 92%
CORVIST		Monosyllables	23/36 64%	20/36 56%
Visual acuity	54/54	Pseudowords	6/24 25%	7/24 29%
Shape discrimination	3/8	Word size(letters)		
Size discrimination	1/2	≤3	21/31 68%	15/31 48%
Hue discrimination	4/4	>3 and ≤5	37/63 59%	16/63 25%
Fragmented numbers	0/8	>5	17/57 30%	21/57 37%
Face perception	6/8	Word type		
Word reading	6/9	Frequent concrete	10/15 67%	4/15 27%
Crowding test	0/4	Infrequent concrete	9/15 60%	7/15 46%
VOSP		Abstract	4/15 27%	5/15 33%
Shape detection screening test	17/20 (15)	Adjectives	4/15 27%	4/15 27%
Incomplete letters	0/20 (16)	Verbs	6/15 40%	6/15 40%
Silhouettes	3/15(15)	Function words	9/15 60%	3/15 20%
Object decision	13/20(14)			
Dot counting	7/10 (8)			
Position discrimination	11/20 (18)			
Number location	5/10(7)			
Cube Analysis	3/9(6)			

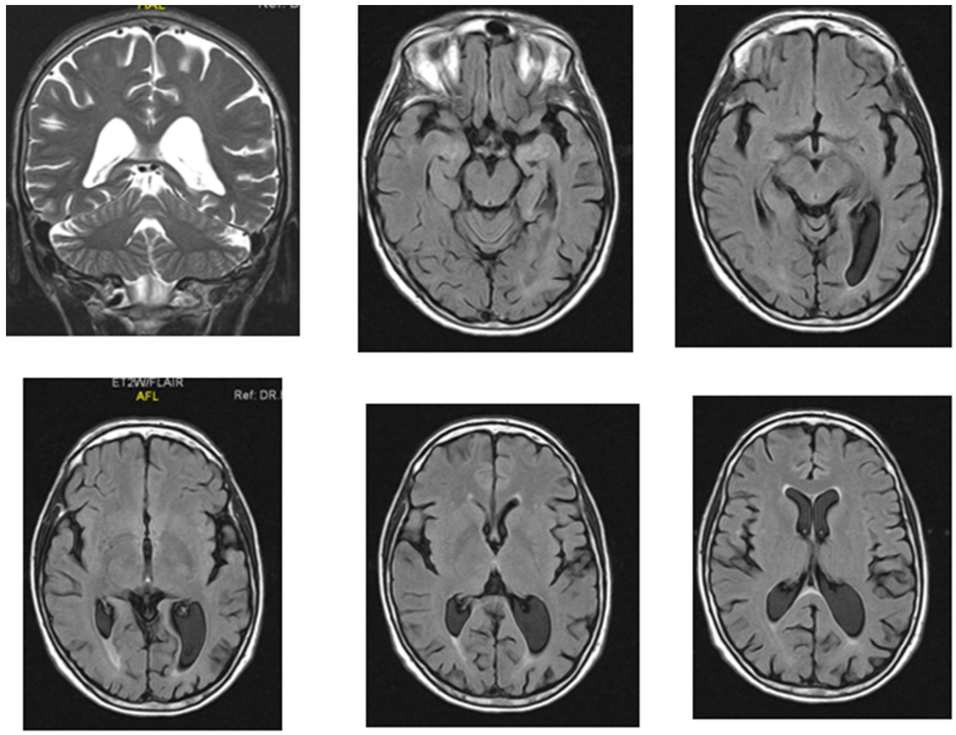


Figure 1

Brain MRI showing a bilateral posterior atrophy, with a dilation of the occipital horns of the lateral ventricles, more marked on the left hemisphere.

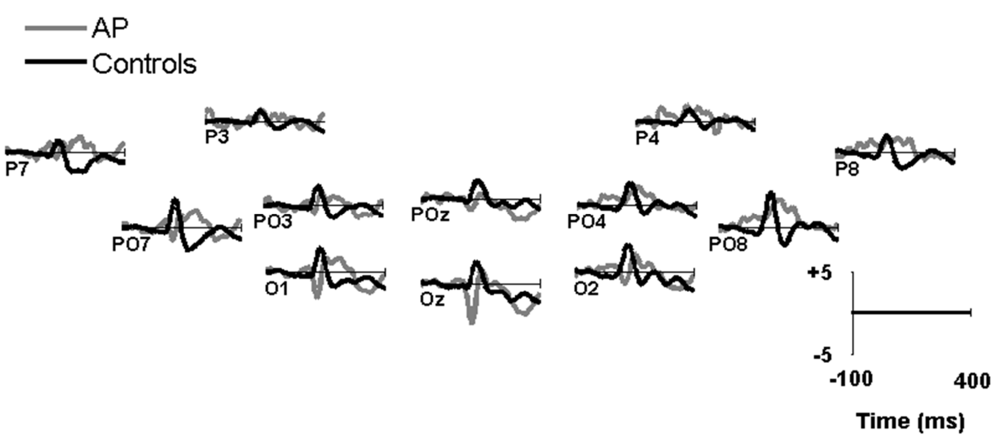


Figure 2

ERP waveforms for word reading in the alexia patient and 15 healthy controls in parieto-occipital channels.

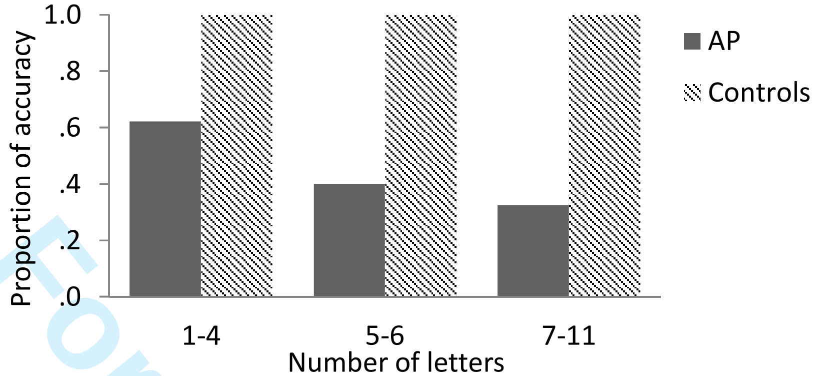


Figure 3

Proportion of correctly read words for each word length category.

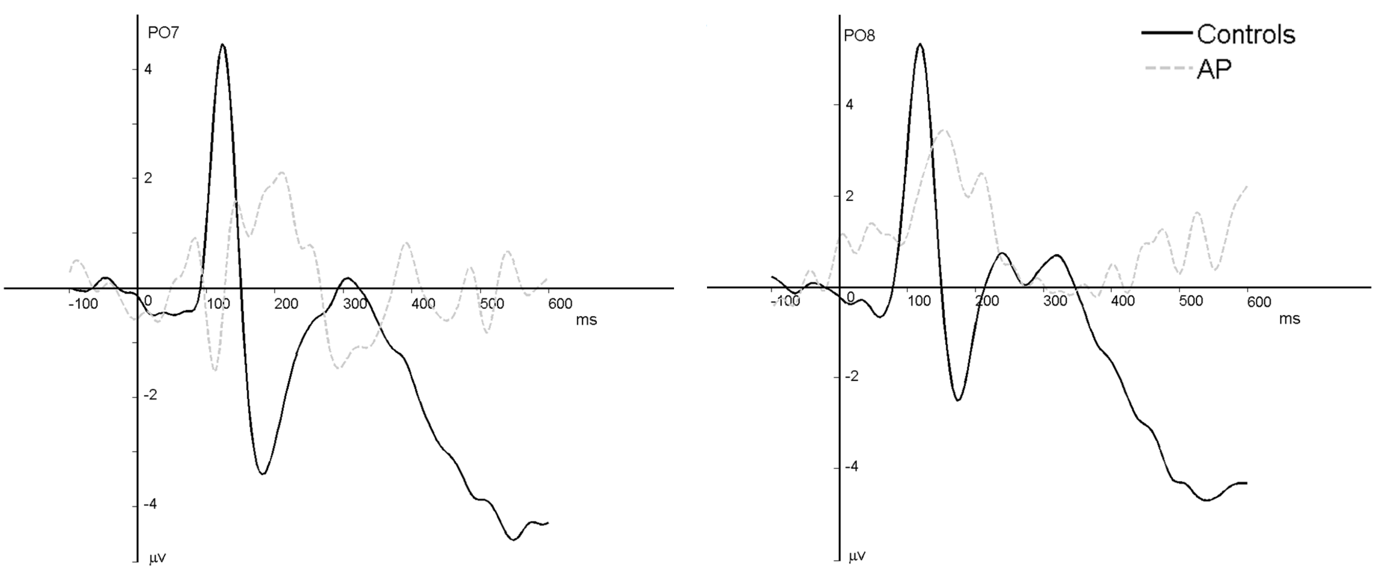


Figure 4

ERP waveforms for word reading in the alexia patient and 15 healthy controls in PO7 and PO8.

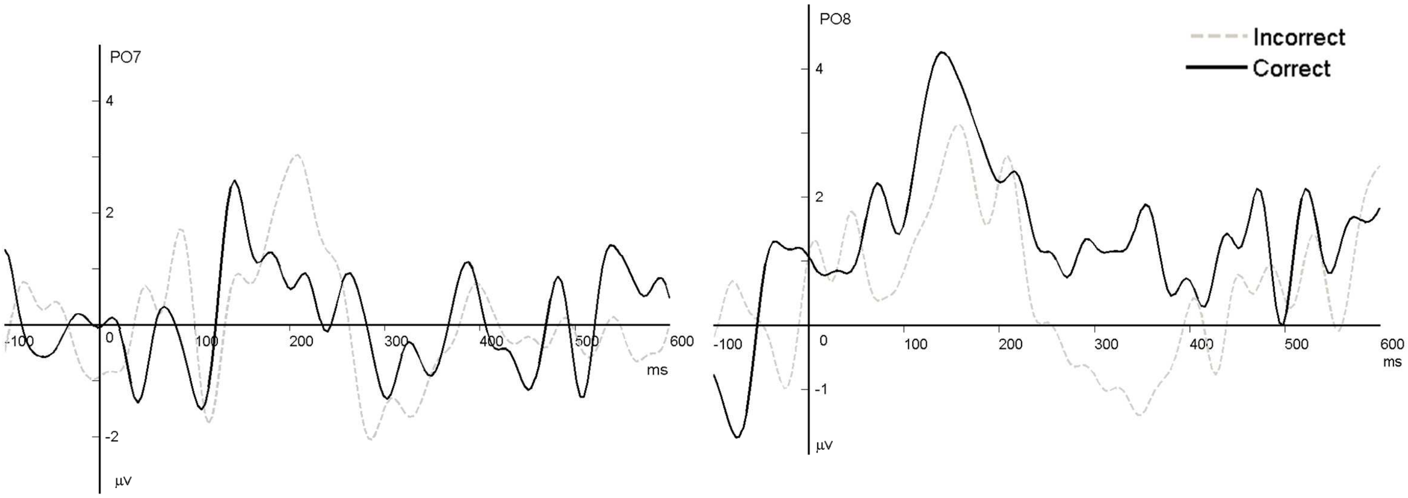


Figure 5

ERP waveforms for words correctly and incorrectly read in AP in PO7 and PO8 electrodes.

Supplemental material

Figure 1b) PET scan showing a bilateral temporo occipital hypo metabolism more marked on the left hemisphere.

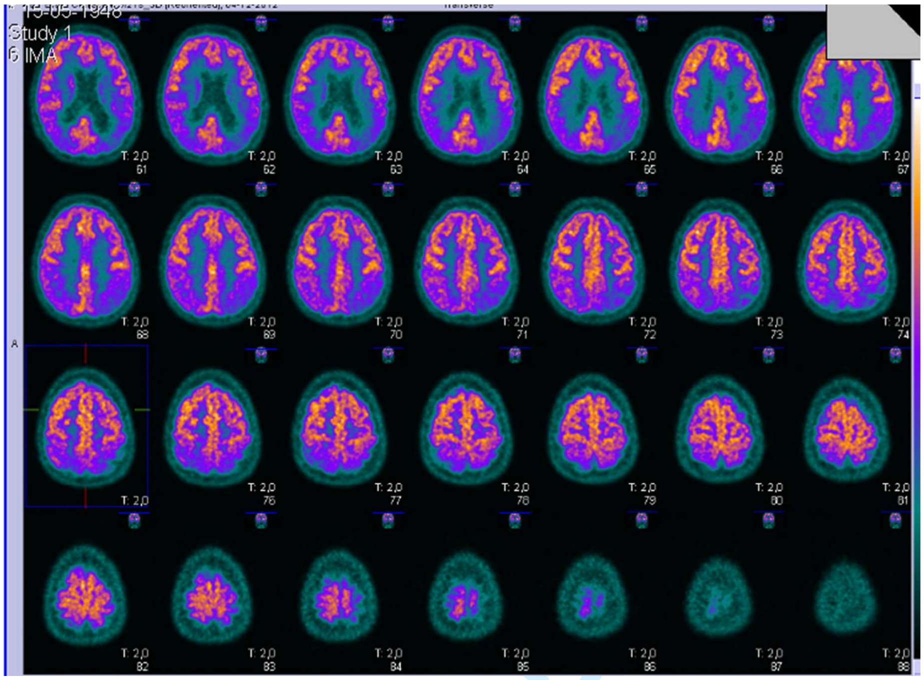
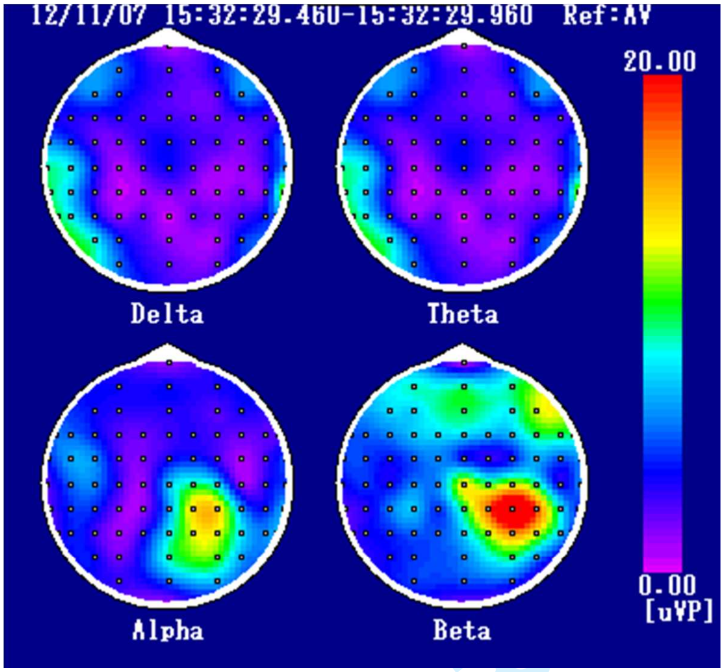


Figure 1c) EEG power spectrum analysis showing a higher power of the slow (theta/delta) frequencies in the left posterior temporal regions



To read or not to read: a neurophysiological study

Running head (max 40 spaces): **ERPs correlates of pure alexia**

Inês Mares [1] , Pedro Custodio [13], José Fonseca [1], Carla Bentes [2], Manuela Guerreiro[1] ,

Nuno Guimarães [3,4] , Isabel Pavão Martins[1]

[1] Language Research Laboratory, Institute of Molecular Medicine (IMM), Faculty of Medicine University of Lisbon (FMUL)

[2]EEG Laboratory, Hospital Sta Maria Centro Hospitalar Lisboa Norte [3], Lisbon Portugal

[3] LASIGE, Faculty of Sciences of the University of Lisbon

[4] ISCTE-University Institute of Lisbon

Corresponding author: I. Pavão Martins, MD PhD; Language Research Laboratory, Department of Neurosciences, Lisbon Faculty of Medicine and Instituto de Medicina Molecular University of Lisbon, Lisboa, Portugal; Telephone/Fax: 351 217 934 480; E-mail: Isabel_Martins@fm.ul.pt

Abstract

Pure alexia (PA) has been associated with visual deficits or~~-~~ a failure to activate the visual word forma area (VWFA). We report a patient~~(AP)~~ with alexia due to posterior cortical atrophy, in whom ERPs revealed a ~~significant~~ delay in the P100 component and an absent N170 compared with controls. Furthermore there was a tendency ~~seemed to be~~for a larger delay in P100 latencies associated with incorrectly read words. This suggests that some cases of PA might result from deficits in visual perception, signaled by the P100 early potential which could lead to an inability to consistently activate the VWFA, marked by the absent N170.

Key words: Alexia, letter-by-letter reading, Posterior cortical atrophy; ERPs

Introduction

Pure alexia, initially described by Dejerine (1982), is characterized by a selective reading impairment in the absence of spoken language or writing deficits. The typical underlying neuroanatomical lesion is localized in the left inferior temporo-occipital region, particularly in the left fusiform gyrus, or in the ~~related to a dis~~connection between that area and the primary visual cortex (Damasio & Damasio, 1983; Dehaene & Cohen, 2011). The severity of this syndrome is variable and some patients retain the ability to read individual words using a strategy called “Letter by letter reading” (LBL), whereby there is an abnormal latency to word production that increases with word length (Behrmann, Plaut, & Nelson, 1998). It has been argued that this behavior might be due to visual impairments (Starrfelt, Habekost, & Leff, 2009). In fact, these patients frequently display concomitant visual deficits and particularly a right hemianopia. Nonetheless, eye-tracking data reveals that patients with pure alexia have increased fixation frequency and longer word reading time in comparison with hemianopic dyslexia patients or virtual hemianopia subjects (Pflugshaupt et al., 2009). Furthermore, differences in damaged areas between those patients seem to indicate the involvement of the visual word form area (VWFA) on pure alexia but~~and~~ not in hemianopic dyslexia (Pflugshaupt, et al., 2009). This area has a selective response to ~~–~~word-like stimuli compared to visual non-orthographic stimuli such as line drawings (Szwed et al., 2011). VWFA has thus been proposed to support visual expertise for printed words allowing their fast and parallel processing (for a review see Dehaene & Cohen, 2011). Studies using both fMRI and ERP (Event Related Potentials) (Brem et al., 2006) or using ERP source analysis (Brem et al., 2006; 2009; Maurer, Brem, Bucher & Brandeis, 2005) have associated ~~related~~ the neural activity of the VWFA to the N170 component of the visual evoked response. Likewise, as in fMRI studies, ERP data has consistently shown an increased N170 amplitude in response to word-like stimuli compared to visual non-orthographic stimuli such as symbol strings (Maurer et al., 2005). Thus, following the presentation of familiar words both VWFA activation and the N170 component should occur and the absence of the N170 component could indicate an impairment of fast or automatic reading.

Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Field Code Changed
Formatted: Font: Not Italic

We report a patient with a posterior cortical atrophy and a progressive reading difficulty, in whom reading was associated with LBL and with delayed and atypical ERPs, particularly for words that she could not read aloud. This case illustrates the potential interest of this technique to the evaluation, diagnosis and characterization of patients with primary reading impairments. It also suggests that the delays in the early visual potentials could lead to a lack of N170 even in correctly read words, further indicating that the residual ability to read in such cases results from the activation of alternative pathways other than through the visual word form area.

Case report

A 64-year-old, right-handed retired female (AP) of Portuguese nationality was evaluated because of a progressive reading impairment beginning 2.5 years before. She had 17 years of formal education and her first language was Portuguese being also fluent in English, French and German due to her academic and professional activity as a translator~~–~~. She first noticed an increasing difficulty in following television or film subtitles as if they were running too fast. Later on, as her reading ability progressively declined, she became unable to read books or even small daily news, due to her effortful and slow performance. She recognized that her memory was not as good as before, but otherwise there were no other complaints, namely of oral language, writing or on daily activities. An ophthalmologic evaluation showed a corrected visual acuity of 7/10 in the right eye, 10/10 in the left eye and a minor loss of the right inferior peripheral visual field sparing the macula. Her past medical history was unremarkable except for frequent migraine attacks with visual aura, for which she had twenty years previously a~~a~~ CT scan performed ~~twenty years~~ with no abnormal findings.

On examination, she showed~~had~~ a fluent speech with a rich vocabulary and an accurate insight to her puzzling reading difficulty, in which~~since~~ she could recognize words as such but ~~she~~ had difficulty processing them. The ~~N~~neurological examination was otherwise normal.

A cognitive assessment (Garcia, 1984; Wechsler, 1997, De Renzi and Vignolo, 1962) revealed a marked visuo-~~-~~spatial impairment. AP presented a normal performance in tests of spoken language (object naming, object identification by name, sentence comprehension, word repetition, syntactic comprehension in the Token test), immediate and working memory (digit span forward and backward), verbal abstraction (proverb interpretation) and writing to dictation or spontaneously. Nonetheless, she had a low age and education adjusted performance on verbal and nonverbal memory tests (logic memory, word pair associates and visual reproduction of the Wechsler Memory Scale) (Garcia, 1984; Wechsler, 1997) and on verbal fluency ~~scores~~ tests (at the level of - 2 standard deviations). Furthermore, she presented severe difficulties in shape and size discrimination and space and form perception (CORVIST and VOSP tests, (Warrington & James, 1991), could not perform the Line Orientation Test (Warrington & James, 1991), presented simultaneo-agnosia during the copy of drawings, had a mild impairment in a test of face recognition (Benton, Hamsher, Varney, & Spreen, 1983), and difficulty recognizing famous faces (20% correct)(Martins, Loureiro, Rodrigues, Dias, & Slade, 2010), although there were~~as~~ no reports of prosop~~o~~agnosia in her daily life. She had a normal score in hue discrimination, could name 80% of colors and identify 100% of colors by name (~~table~~ Table 1 for the visuo-~~-~~spatial examination). ~~Although~~ Even though she could easily write numbers and perform mental calculations, she could only name 56% of Arabic numbers and could not read roman numbers, which she did before.

Insert Table 1 here

AP could easily write letters and words to dictation, copy letters, match capital letters and match printed with handwritten letters without errors. She was also easily capable of spelling out words and reconstructing words orally from dictated letters, excluding a central reading disorder.

She could read aloud and identify single letters in multiple choice, but presented a word length effect with a worse performance as the number of letters increased. She read 100% of single letters, 68% on ≤3 letter words, 59% on 4-5 letter words and 30% on >5 letters words (see T~~t~~able 1

for reading examination). Her reading performance was compared between English, French and and her native Portuguese language with a new set of 15 stimuli in each language matched for word length. She read correctly 26.6% French words but produced 33% French paralexias (riviére- revanche; chaise- chasse; poulet- pauvre) and~~;~~ read correctly 40% English words ~~and~~ producing~~ed~~ 33% English morphologic paraphasias (nose - mouse; car - can, foot - photo). In Portuguese, she correctly read 26.6% of the 15 words and produced 73% Portuguese paralexias, of which 63.6% were semantic (nariz (nose) – mês (month); carro (car) – campo (field); fato (suit) – tecto (ceiling)) and 36.4% phonological (pão (bread)– rão; copo (glass) – compe; café (coffee) – cavés).

A brain MRI (Figure 1a) demonstrated an atrophy of the posterior regions of both hemispheres with a dilation of the occipital horns of the lateral ventricles and an F-FDG Pet scan showed a bilateral occipital and temporal hypo metabolism more marked on the left hemisphere (Figure 1b SUP).

Insert Figure 1a here

A 72 channel EEG (international 10/20 electrode placement system) was performed using a Nihon-Kohden system (Neurofax - EEG 1200). Electroencephalographic background activity showed a dominant alpha rhythm with superimposed irregular and low amplitude theta bursts over the left temporal regions. In several recording periods, an asymmetry (higher than 50%) of the posterior alpha activity was documented suggesting a left posterior dysfunction. Furthermore, in the power spectrum analysis, there was a right posterior quadrant dominance of ~~the~~ fast (alfa/beta) activities and a higher power of the slow (theta/delta) frequencies in the left posterior temporal regions (Figure 1cSUP).

Experimental reading tasks and ERPs (Event R~~r~~elated P~~p~~otentials) evaluation

EEG was recorded while AP performed a single word reading task controlled for word frequency, grammatical class and word length. ERPs waveforms were compared to a control group of 15 participants (9 males and 6 females), with ages ranging from 23 to 35 years ~~old~~ (M = 27.75 years) and no language disorders. Written informed consent was given by all participants. The consent form was read to the patient by her husband.

Stimuli consisted of a list with 129 words ~~list~~, divided in three classes (43 words each): function words, concrete content words and abstract content words (Marques, Fonseca, Morais, & Pinto, 2007). All classes were matched by word frequency (M=924.91±923.95 frequency in a 16.210.438 word corpus; Bacelar do Nascimento, 2001), and word length (M=6.07±1.70 letters). Word class did not differ in frequency (F(3,168)=.13, ~~MSE= 956137,36~~ p=.94) nor word length (F(3,168)=.47, ~~MSE=2.61~~ p=.71). Given time constraints, 189 trials were presented randomly chosen from the above list, with each word being displayed at least once and no more than twice (60 repeated words).

Field Code Changed

Field Code Changed

Individual words were displayed centrally during one second in which the patient was instructed not to read aloud. After that~~, the word remained on screen and a~~ a red dot appeared, while the word remained on screen, indicating that the patient should try to read the word aloud. The word and the red dot remained on screen until response for a maximum of 10 seconds, with an inter stimulus interval of 500 ms.

All ~~other~~ participants did the same procedure~~,~~ varying only the number of trials drawn in the same manner from the initial list (due to technical issues 8 participants ~~did~~performed 129 trials and 7 only did 60 trials).

ERP recording and analysis.

Brain electrical activity was obtained with the same EEG system described above, online referenced to the mastoids at a sampling rate of 1000 Hz. Impedances were kept below 10 kΩ. Data was

afterwards downsampled to 256 Hz and re-referenced to the average of all electrodes. Data was band-pass filtered at 0.1-30Hz. Continuous data was epoched between -100 and 600 ms relative to the onset of word display, using the ~~first~~ -100 ms previous to word onset as baseline. Artifacts were automatically rejected using EEGLAB (Delorme & Makeig, 2004). Twenty-seven percent of trials were rejected for AP. An average of 7.5% of trials was rejected for controls. When comparing correctly and incorrectly read words on AP, 78 and 111 trials were included for each category respectively. After trial rejection 57 trials were kept for correctly read words, and 81 for words not read. Analysis of the P100 and N170 potentials focused on posterior occipital electrodes (Figure 2). Maximum amplitude for these two components was found on PO7 and PO8, and this electrode pair was selected for further analysis.

Field Code Changed

Insert Figure 2 here

~~For the controls, the m~~Mean latency of the P100 was obtained, for controls, at a time window ranging frome ~~of~~ 98.56 ~~-~~to 158.56 ms. This range~~–~~ corresponded to - 20/+40 ms around the maximum amplitude of the P100 component on the grand averaged ERP. Since in AP the P100 was more dispersed, peak latency was determined in her case as the maximum peak between 117 ms and 254 ms.

These measures were then subjected to statistical analysis with a ~~modified~~ t-test modified for comparing single cases with relatively small samples (Crawford & Porter, 2002), used here to compare patient's latency of P100 on word reading with the control group. To compare correct and incorrect trials in AP, a bootstrap single-subject ~~analyses~~analysis was used. The difference between peak latencies in the above time window was used as the correct and incorrect contrast. This technique creates a large number of resampled datasets with the same number of trials per condition as before. For this, each trial is taken in a random and independent way, with

replacement, from the original dataset. Differences between correct and incorrect peak latencies where calculated from 50 000 resampled datasets. Results were considered significant if the 5th percentile of the differences distribution was above 0, meaning at $p>.05$ (one-tailed).

Results

Behavioral results

AP had 41% accuracy in 189 words while all other participants had 100% accuracy (Figure 2). Accuracy did not depend of word type (function words, verbs, abstract and concrete words; $F(2,186)=1.176$, $p=.311$) nor word frequency divided in three groups (<1000 frequency in lexical corpus, 1001-2000, >2001; $\chi2$ (2) = 1.46, p = .482), but the typical word length effect was shown between 3 word length groups (3-4 letters, 5-6 letters, 7-11 letters; $\chi2$ (2) = 9.18, p = .01).

Insert Figure 3 here

Event related potentials

Compared to controls, the patient had delayed and less clear ERPs in response to single word presentation (Figure 4). Furthermore there was a significant difference in the latency of the first evoked response latency (P100) between patient and controls on both occipital electrodes PO7 ($t(14)$ = 7.76, $p<.001$) and PO8 ($t(14)$ = 3.05, $p=.009$). After the first initial component, there ~~is~~ was a negative component (N170) in the controls' ERPs that is not clearly present on the patient's ERPs.

Insert Figure 4 here

Comparing the waveforms on AP between correct and incorrectly read words ~~that correctly read and~~ , the P100 component seemed to divide in an earlier and later component respectively (Figure 5), with a tendency for a faster waveform in association with words the patient could read.

This difference did not reach statistical significance in PO8 although there was a non-significant trend in PO7 ($p=.08$). No amplitude differences were found. Responses to words c~~C~~orrectly read ~~words in~~ by AP were also compared with those of~~e~~ 7 participants that had a similar number of trials (<60) on the PO7 electrode. In this comparison, P100 peak on correctly read words in AP (126.9 ms) did not show ~~no longer showed~~ a significant delay compared with controls ($t(6) = 2.0$, $p=.09$). Nonetheless incorrectly read words in AP showed a later P100 peak (208.3 ms) when compared with controls ($t(6) = 10.8$, $p<.001$).

Insert Figure 5 here

Discussion

We report the case of a 64 year old woman with a pure alexia due to a posterior cortical atrophy ~~(PCA)~~ who presented abnormal electrophysiological response to words~~,~~ and in whom P100 showed a delayed P100 peak compared to controls~~, and in whom ERPs were different between words she could read or could not read~~. To our knowledge the current study is the first to report ERP correlates in pure alexia due to posterior cortical atrophy. Furthermore it is ~~one of the few~~the second ERP studies of pure alexia, ~~with the exception of~~after Neville, Snyder, Knight and Galambos (1979) who reported three patients with alexia and their ERP correlates.

Field Code Changed

Field Code Changed

AP presented with an insidious steady and progressive difficulty in reading, associated with marked visuo-perceptive and visuo-spatial impairments, in the absence of a primary ophthalmologic disorder, an intact insight ~~for the~~of her situation, an MRI documenting posterior cortical atrophy and a bilateral occipito-temporal hypometabolism, more marked on the left hemisphere. These features are in accordance with the proposed diagnostic criteria for posterior cortical atrophy~~PCA~~ (Kas et al., 2011; McMonagle, Deering, Berliner, & Kertesz, 2006; Mendez, Ghajarania, & Perryman, 2002; Tang-

Field Code Changed

Field Code Changed

Field Code Changed

Formatted: Portuguese (Portugal), Check spelling and grammar

Formatted: Portuguese (Portugal), Check spelling and grammar

Wai et al., 2004), with a predominance of ventral visual dysfunction. Cognitive assessment also disclosed a minor anterograde episodic memory defect and a low verbal fluency as is usual in posterior cortical atrophy~~PCA~~ (Kas, et al., 2011).

Field Code Changed

Formatted: Portuguese (Portugal), Check spelling and grammar

AP reading performance was consistent with a peripheral alexia, since she could spell out words and reconstruct words from dictated letters. She also presented a word length effect that is usual in pure alexia. The bilateral dysfunction of the ventral occipital temporal cortex does not allow the identification of a circumscribed area responsible for reading impairment. Yet the preservation of writtening~~ing~~ and spoken language, the lack of a word class or regularity effect, the ability to read letters and the word length effect suggest that the disorder is at the level of word form recognition. This could result either from a disorder of the ~~is region~~ VWFA itself or from a failure of its activation. Interestingly she had some word form information about incorrectly read words ~~she could not read since she produced~~ producing paraphasic errors within the stimuli specific language.

ERPs obtained during reading showed~~, in comparison with age matched controls,~~ a delayed cortical response to printed words, involving the first cortical components, which suggests~~ing~~ a primary cortical visual disturbance~~,~~. ~~which~~This is in accordance with what is known about the pathology of posterior cortical atrophy, with typical visual deficits. ~~AP,~~AP had a delayed P100~~,~~ and an absent N170. The current results differ from Neville, Snyder, Knight and Galambos (1979) who report for patients with alexia, alterations mostly at the N170 component sparing the P100. This data was collected at posterior sites (P3 and P4) from three patients with different etiologies but not posterior cortical atrophy. The differences found might suggest that different etiologies, and particularly posterior cortical atrophy, might have different underlying deficits as supported by ERP correlates.

Field Code Changed

In addition, ERPs in AP suggest an increased latency and wave disorganization in response to the stimuli that the patient could not read aloud, but a more typical response to the words the patient could read aloud not differing in P100 latency when compared with controls. Nonetheless

due to the reduced number of trials no significant differences could be found between read and not read words in AP.

The known N170, associated with word reading and VWFA activation was absent confirming an early impairment of word processing. The lack of this component might be a further suggestion of its importance in the clinical symptoms of pure alexia. It could also suggest that this patient was using alternative pathways to read, such as an orthographic phonologic conversion, but the lack of a regularity effect and a word length effect do not support this hypothesis.

Formatted: Indent: First line: 0.49"

These results document a neurophysiological correlate of visual dysfunction in posterior cortical atrophy. The pathophysiology of peripheral alexias in posterior cortical atrophy is controversial. While some authors attribute reading difficulties to the primary visual impairment leading to an inability to activate the cascade serial visual processing ~~to the level of lexical and semantic representations necessary to read~~, others showed that reading can be dissociated from visual disturbances and might have no causal relation with it (Yong, Warren, Warrington, & Crutch, 2013).

Field Code Changed

We acknowledge some limitations to this study. Data from ~~As~~ a single case study ~~it~~ is difficult to generalize, especially since the use of ERP methodology usually relies on the grand-average of waveforms across participants. However, posterior cortical atrophy is an unusual form of presentation of degenerative brain disorders and rarely ~~it most often does not~~ presents with a pure alexia but rather with dorsal stream disorders, like optic ataxia and Balint syndrome. ~~Secondly,~~ In addition, it was not possible to obtain a large~~r~~ number of trials due to the patient inability to sustain long sessions of reading tasks. The latter ~~ese two factors~~ contributes to waveforms with more noise in AP when compared with ~~the~~ controls' grand average. Nonetheless, even in participants' individual data with less trials and more noise, it was still possible to identify an earlier P100 and a normal N170, suggesting that differences in AP can't be attributed just to these limitations.

This case shows that, in posterior cortical atrophy, the pattern of response to printed material is variable suggesting that an early and fast activation of the primary cortical areas, as demonstrated by a normal latency in P100, can lead to a more effective activation of the visual word form area leading to an accurate response. It also suggests that in early posterior cortical atrophy the response of the occipito temporal cortex might be crucial for correct reading. Although there are no clear results regarding the difference between correct and incorrectly read words, when compared with controls the data suggests that a fast perception might facilitate the activation of a possibly dysfunctional visual word form area.

Although this report has the limitations of a single case study it suggests the visual cortical ERP might be useful in the diagnosis of peripheral alexias and might contribute to document the pattern of impairment in patients with inconsistent responses or without documented brain lesions in imaging.

Acknowledgments

This study was supported by a grant from Fundação para a Ciência e Tecnologia Portugal. RAPS. Reading Analysis with neuroPhysiological Signs, FCT. Coordinator: N. Guimarães. PTDC/EIA-EIA/113660/2009.

References

Bacelar do Nascimento, M. F. (2001). Um novo léxico de frequências do português *Homenagem ao Professor Herculano de Carvalho* (pp. prelo).

Behrmann, M., Plaut, D. C., & Nelson, J. (1998). A literature review and new data supporting an interactive account of letter-by-letter reading. *Cognitive Neuropsychology, 15*, 7-51.

Benton, A., Hamsher, K., Varney, N., & Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual*. New York, USA: Oxford University Press.

Brem,S., Bucher, K., Halder, P., Summers, P., Dietrich, T., Martin, E., & Brandeis. D. (2006). Evidence for developmental changes in the visual word processing network beyond adolescence. *NeuroImage,29*(3), 822-837. doi:10.1016/j.neuroimage.2005.09.023

Brem, S., Halder, P., Bucher, K., Summers, P., Martin, E., & Brandeis, D. (2009). Tuning of the visual word processing system: distinct developmental ERP and fMRI effects. *Human brain mapping, 30*, 1833-1844. doi: 10.1002/hbm.20751

Crawford, J. R., Garthwaite, P. H., & Porter, S. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia*, *40*, 1196-1208.

Damasio, A. R., & Damasio, H. (1983). The anatomic basis of pure alexia. *Neurology, 33*(12), 1573-1583.

De Renzi, A., & Vignolo, L. A. (1962). Token test: A sensitive test to detect receptive disturbances in aphasics. *Brain, 85*, 665–678.

Dehaene, S., & Cohen, L. (2011). The unique role of the visual word form area in reading. *Trends in cognitive sciences, 15*, 254-262. doi: 10.1016/j.tics.2011.04.003

Dejerine J. (1892). Contribution à l'étude anatomo-pathologique et clinique des différentes variétés de cécité verbale. *Mémoires de la Société de Biologie; 4*, 61–90.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods, 134*(1), 9-21. doi: 10.1016/j.jneumeth.2003.10.009

Garcia, C. (1984). *A doença de Alzheimer. Problemas de diagnóstico clínico.* Tese de Doutoramento, Faculdade de Medicina da Universidade de Lisboa, Lisboa.

Kas, A., de Souza, L. C., Samri, D., Bartolomeo, P., Lacomblez, L., Kalafat, M., . . . Sarazin, M. (2011). Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain, 134*(Pt 5), 1464-1478. doi: 10.1093/brain/awr055

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: HTML Preformatted, Indent: Left: 0", First line: 0"

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Not Italic

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: +Body (Calibri), 12 pt

Formatted: Font: +Body (Calibri), 11 pt

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Indent: Left: 0", First line: 0"

Formatted: English (U.K.)

Formatted: Font: (Default) +Body (Calibri), English (U.K.)

Formatted: Font: +Body (Calibri), 11 pt, English (U.S.)

Formatted: Font: +Body (Calibri), 11 pt, Not Italic, English (U.S.)

Formatted: Font: +Body (Calibri), 11 pt, English (U.S.)

Formatted: Font: +Body (Calibri), 11 pt

Formatted: Font: +Body (Calibri), 11 pt, Not Italic

Formatted: Font: +Body (Calibri), 11 pt

Formatted: Font: +Body (Calibri), 11 pt, Portuguese (Portugal)

Formatted: Font: +Body (Calibri), 11 pt, Not Italic

Formatted: Font: +Body (Calibri), 11 pt

Formatted: Font: +Body (Calibri), 11 pt, Not Italic

Formatted: Font: +Body (Calibri), Italic, Portuguese (Portugal)

Formatted: Portuguese (Portugal)

Marques, J. F., Fonseca, F. L., Morais, a. S., & Pinto, I. a. (2007). Estimated age of acquisition norms for 834 Portuguese nouns and their relation with other psycholinguistic variables. *Behavior research methods, 39*, 439-444.

Martins, I. P., Loureiro, C., Rodrigues, S., Dias, B., & Slade, P. (2010). Factors affecting the retrieval of famous names. *Neurological sciences, 31*, 269-276. doi: 10.1007/s10072-009-0176-x

Maurer U, Brem S, Bucher K, Brandeis D. (2005). Emerging neurophysiological specialization for letter strings. *Journal of Cognitive Neuroscience*, *17*(10):1532–1552.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. Trends in *Cognitive Sciences, 7*, 293-299. doi: 10.1016/S1364-6613(03)00134-7

McMonagle, P., Deering, F., Berliner, Y., & Kertesz, A. (2006). The cognitive profile of posterior cortical atrophy. *Neurology, 66*(3), 331-338. doi: 10.1212/01.wnl.0000196477.78548.db

Mendez, M. F., Ghajarania, M., & Perryman, K. M. (2002). Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. *Dement Geriatr Cogn Disord, 14*(1), 33-40. doi: 58331

Neville, H., Snyder, E., Knight, R., & Galambos, R. (1979). Event-related potentials in language and non-language tasks in patients with alexia without agraphia. . In Lehmann & Callaway (Eds.), *Human evoked potentials* (pp. 269-283). New York: Plenum Press.

Pflugshaupt, T., Gutbrod, K., Wurtz, P., von Wartburg, R., Nyffeler, T., de Haan, B., . . . Mueri, R. M. (2009). About the role of visual field defects in pure alexia. *Brain, 132*(7), 1907-1917. doi: 10.1093/brain/awp141

Starrfelt, R., Habekost, T., & Leff, A. P. (2009). Too little, too late: reduced visual span and speed characterize pure alexia. *Cerebral cortex (New York, N.Y. : 1991), 19*, 2880-2890. doi: 10.1093/cercor/bhp059

Szwed M, Dehaene S, Kleinschmidt A, Eger E, Valabregue R, et al. (2011). Specialization for written words over objects in the visual cortex. *Neuroimage, 56*, 330–344. doi: 10.1016/j.neuroimage.2011.01.073.

Tang-Wai, D. F., Graff-Radford, N. R., Boeve, B. F., Dickson, D. W., Parisi, J. E., Crook, R., . . . Petersen, R. C. (2004). Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology, 63*(7), 1168-1174.

Warrington, E. K., & James, M. (1991). *The visual object and space perception battery.* Bury St. Edmunds: Thames Valley Test Company.

Wechsler, D. (1997). *Wechsler Memory Scale-Third Edition (WMS-III)*. San Antonio, TX: The Psychological Corporation.

Yong, K. X., Warren, J. D., Warrington, E. K., & Crutch, S. J. (2013). Intact reading in patients with profound early visual dysfunction. *Cortex*. doi: 10.1016/j.cortex.2013.01.009

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: citation, Indent: Left: 0", Hanging: 0.5"

Formatted: Font: 11 pt

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, Italic, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, Italic, English (U.S.), Do not check spelling or grammar

Formatted: Font: Calibri, 11 pt, English (U.S.), Do not check spelling or grammar

Formatted: Font: Not Italic

Formatted: Font: +Body (Calibri)

Formatted: Font: English (U.S.)

Formatted: Font: Italic

Formatted: Font: Italic

Formatted: Font: (Default) Times New Roman, 12 pt, English (U.S.)

Formatted: element-citation, Font: (Default) Times New Roman, 12 pt, English (U.S.)

Table 1. Visuo spatial and reading evaluation.

Visuo spatial examination		Reading examination		
Tests	Score/Max 19-07-2013 (5% cut-off)	Tests	11/10/12 Score/Max	07/05/13 Score/Max
Benton facial recognition	36/54	Arabic Numbers	10/18	6/18
Naming famous faces	15/74	Roman numbers	0/5	1/5
Object visual Naming	14/16	Letters	12/12 100%	11/12 92%
CORVIST		Monosyllables	23/36 64%	20/36 56%
Visual acuity	54/54	Pseudowords	6/24 25%	7/24 29%
Shape discrimination	3/8	Word size(letters)		
Size discrimination	1/2	≤3	21/31 68%	15/31 48%
Hue discrimination	4/4	>3 and ≤5	37/63 59%	16/63 25%
Fragmented numbers	0/8	>5	17/57 30%	21/57 37%
Face perception	6/8	Word type		
Word reading	6/9	Frequent concrete	10/15 67%	4/15 27%
Crowding test	0/4	Infrequent concrete	9/15 60%	7/15 46%
VOSP		Abstract	4/15 27%	5/15 33%
Shape detection screening test	17/20 (15)	Adjectives	4/15 27%	4/15 27%
Incomplete letters	0/20 (16)	Verbs	6/15 40%	6/15 40%
Silhouettes	3/15(15)	Function words	9/15 60%	3/15 20%
Object decision	13/20(14)			
Dot counting	7/10 (8)			
Position discrimination	11/20 (18)			
Number location	5/10(7)			
Cube Analysis	3/9(6)			

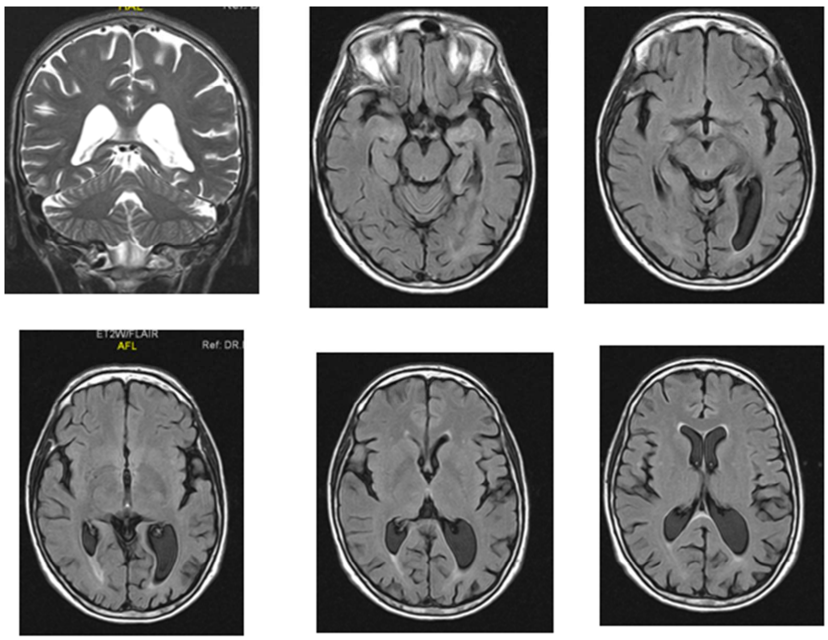


Figure 1

Brain MRI showing a bilateral posterior atrophy, with a dilation of the occipital horns of the lateral ventricles, more marked on the left hemisphere.

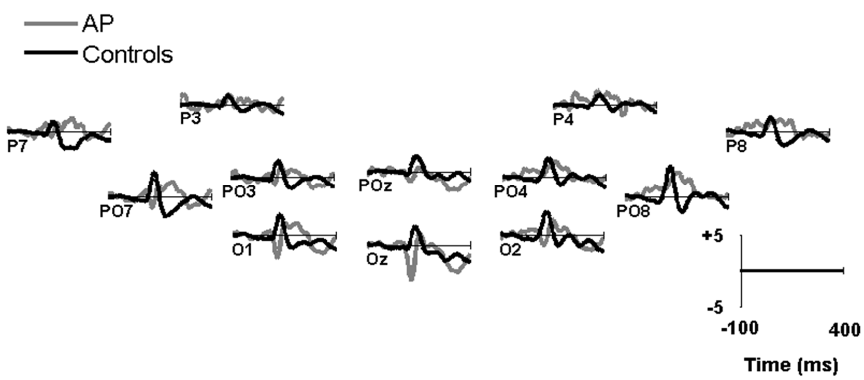


Figure 2

ERP waveforms for word reading in the alexia patient and 15 healthy controls in parieto-occipital channels.

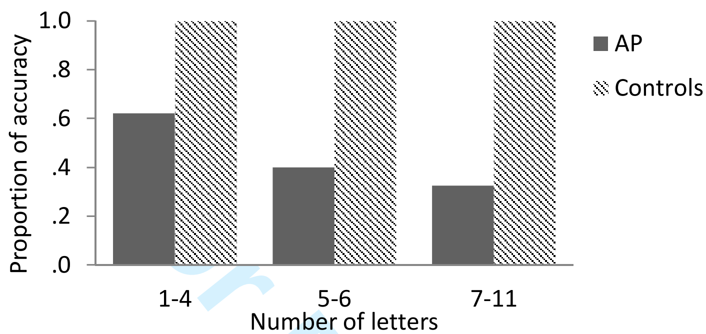


Figure 3

Proportion of correctly read words for each word length category.

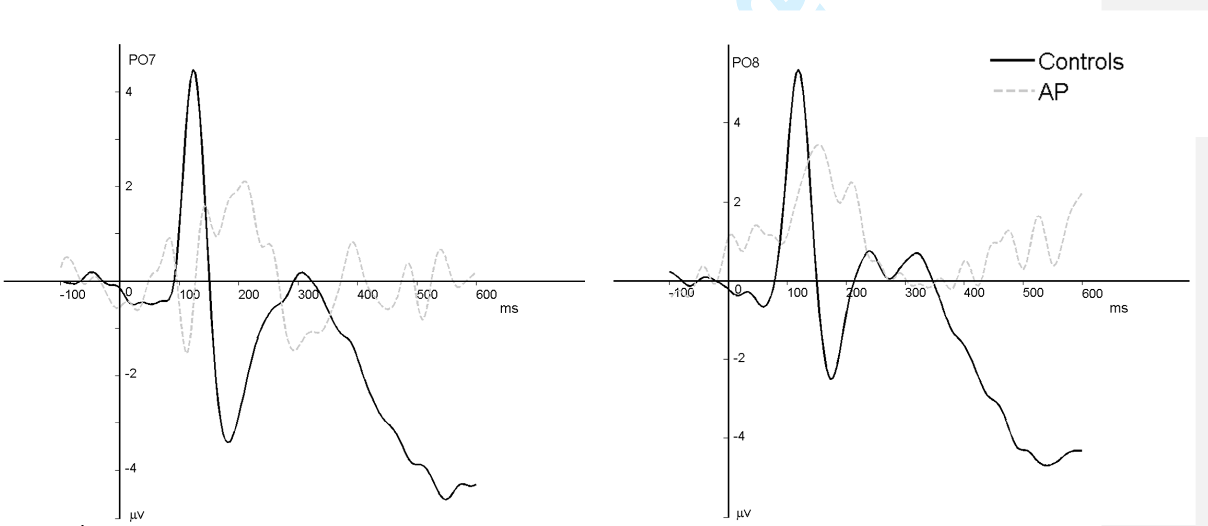


Figure 4

ERP waveforms for word reading in the alexia patient and 15 healthy controls in PO7 and PO8.

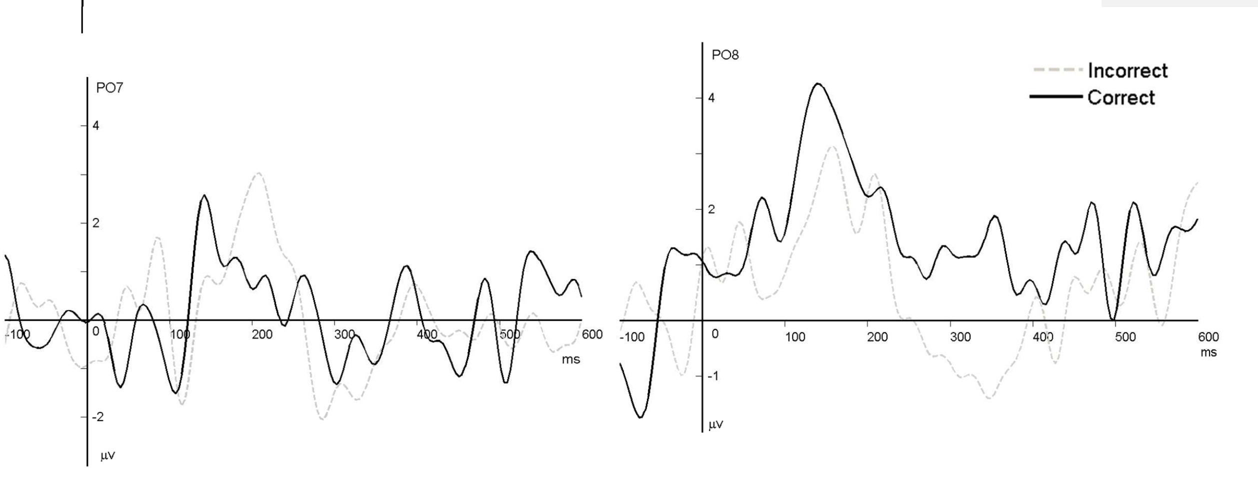


Figure 5

ERP waveforms for words correctly and incorrectly read in AP in PO7 and PO8 electrodes.