CASE STUDY

ACTA Vol. 18, No. 3, 2020, 313-325
NEUROPSYCHOLOGICA

Received: 18.01.2020
Accepted: 01.07.2020

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

FUNCTIONAL NEUROMARKERS OF COGNITIVE IMPAIRMENT IN VASCULAR DEMENTIA: A CASE STUDY

Marzena Supińska[1(A,B,D,E)], Jolanta Górla-Półrola[2(A,B,D,E)], Ksenia Cielebąk[3(A,B,C,D)], Izabela Herman-Sucharska[4(A,B,D,E)], Juri D. Kropotov[5(A,B,D,E)], Maria Pąchalska[3(A,B,D,E,F)]

[1] Department of Physiotherapy, Academy of Physical Education, Wroclaw, Poland
[2] Old Polish University, Kielce, Poland
[3] Chair of Neuropsychology and Neurorehabilitation, The Andrzej Frycz-Modrzewski Cracow University, Kraków, Poland
[4] Department of Electroradiology, CMUJ, Krakow, Poland
[5] N.P. Bechtereva Institute of the Human Brain of Russian Academy of Sciences, Saint-Petersburg, Russia

SUMMARY

Background: Early diagnosis and monitoring of disease progression in patients with Vascular Dementia (VaD) have become vital in clinical practice, as disease modifying treatments for VaD become available. The goal of our research was to study cognitive impairment in a patient at an early stage of VaD. We evaluated latencies of the P3 GO and NOGO components of event-related potentials (ERPs), elicited in cued GO/NOGO tasks, as potential neuromarkers of cognitive impairment, as suggested by previous research.

Case study: The patient, a right-handed, 53-year-old male with a college education, suffered a transient ischemic attack (TIA) in 2011. During this attack, which lasted for a few minutes, he was confused and had trouble speaking, trouble seeing in both eyes, difficulty walking, problems with balance and coordination, and strange behavior. Seven years later, in 2018, he was assessed using the HBI methodology, which consisted of recording (1) a 19-channel EEG in resting state (with eyes open and eyes closed), and (2) a cued GO/NOGO task, and then comparing the results with EEG spectra and Event-Related Potentials (ERPs) data from normative and patient databases. The patient died in 2019. Post-mortem studies confirmed cortical microhaemorrhages neuropathological criteria for VaD. We did not found deposits of hyperphosphorylated tau (HPт) and Aβ, which fulfil the neuropathological criteria for AD.

Results: The parietal-temporal-occipital EEG power was significantly higher in all conditions in this subject in comparison to healthy controls, indicating idling of the corresponding areas. The amplitude and latency of the P3 GO wave were found to be intact in the subject, indicating normal posterior cortical functioning in the cognitive task. The latency of the P3 GO wave was found to be significantly higher in the subject, indicating impairment of engagement operations.

Conclusions: In a GO/NOGO task, ERPs provide a useful tool for assessment of brain functioning in clinical settings.

Key words: Cognitive impairment, Quantitative Electro-Encephalogram (QEEG), Event-Related Potentials (ERPs), cued GO/NOGO task

INTRODUCTION

Late positive fluctuations of event-related potentials in oddball and GO/NOGO paradigms are reliable indices of normal aging [1,2,3,4,5,6]. Numerous studies have demonstrated that these potentials constitute a family of functional neuromarkers reflecting different aspects of cognitive control. Indeed, P3 b waves in response to rare targets in the oddball paradigm and P3 GO waves in the GO/NOGO paradigm show a parietal distribution at latencies around 300 ms [1]. These parietally distributed P3 waves decrease in amplitude and increase in latency in normal aging [2]. In contrast, the P3 NOGO waves in the GO/NOGO paradigm show central-frontal distribution and increase in amplitude in normal aging [3,5]. The functional meaning of these ERP components has not been definitively described, but many researchers would agree that the parietal P3 target (P3 GO) wave reflects an engagement operation, namely a re-activation of stimulus-response associations of the prepotent model of behavior, while the frontal-central NOGO components reflect subcomponents of cognitive control, such as conflict detection and monitoring, as well as prepared action inhibition [2,5,6].

The parietal P3 target (P3 GO) and frontal-central P3 NOGO have been shown to decrease in amplitude in dementia and to increase in latency in comparison to healthy controls [2]. These data, together with the above-mentioned evidence about the distinct functional meaning of P3 components, demonstrate that there are two different types of dysfunction in dementia, frontal and posterior, with different localizations and different functional meanings. In this study we applied the Human Brain Index (HBI) database [1,2] in order to determine the type of brain dysfunction in a case of vascular dementia (VaD).

CASE STUDY

The patient, a right-handed male, 53 years old, with a college education, had a transient ischemic attack (TIA) in 2011, and was treated in the Department of Vascular Surgery and Endovascular Procedures at the John Paul II Hospital, in Krakow, Poland. During the attack, which lasted for a few minutes, he was confused and had trouble speaking, trouble seeing in both eyes, difficulty walking, problems with balance and coordination, and odd behaviour. All symptoms resolved after a few hours. A year later, the patient was referred to the neurology department because of double vision, which resolved after two weeks of treatment. Because the patient complained about the deterioration of attention and memory, he was referred for a neuropsychological examination.

MRI examination (2011)

MRI studies in 2011 (first examination) showed discrete cortical atrophy and vascular white matter lesions (Fig.1 A and B).

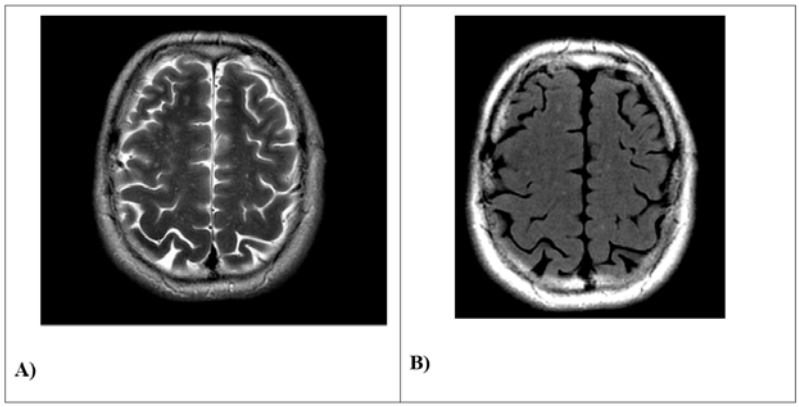

Fig. 1A and B. Brain MRI: A) frFSET2, B/FLAIRT2, axial plane. Signs of discrete cortical atrophy in the coronal and occipital regions on both sides. Punctate hyperintensive foci in the subcortical white matter of the both brain hemispheres indicating small vessel disease.
Source: own research

First neuropsychological examination

A neuropsychological examination carried out in 2011 showed the following:

1. No evidence of any form of dementia described in DSM-5, regardless of etiology (MMSE = 26 points);
2. No evidence of emotional disorder, schizophrenia, alcoholism, addiction to legal medications or illegal drugs, Parkinson's Disease, epilepsy, disordered consciousness, or intellectual impairment, either found at the time of examination or documented in the medical history;
3. No disorders of movement, vision, or hearing that might interfere with his compliance with any of the instructions and procedures that would be used in the clinical tests;

We found no indication of any other serious somatic diseases, including during the decompensation phase.

MRI examination (2018)

Seven years later, in 2018, he had a second TIA which lasted a few minutes. **MRI studies in 2018** (second examination) **showed secondary vascular demyelination** (fig. 2 A and B).

Second neuropsychological examination (2018)

In neuropsychological testing the Hachiński Ischemia Scale result was 2 points; second stage on the Global Deterioration Scale (GDS; headaches, dizziness, balance disorders) and neuropsychological symptoms (concentration and selectivity of attention; memory disorders (memory dynamics, reproduction of geometric figures), depression and emotional disorders (severe anxiety), and behavioral disorders (apathy, hypersensitivity, irritability) [12,13]. In neuropsychological testing we found that the MMSE score had deteriorated to 18 points, which is mild de-

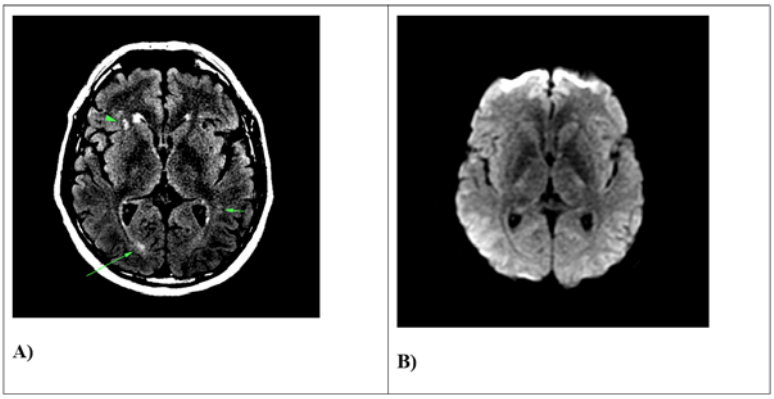

Fig. 2 A and B. Brain MRI: A/FLAIRT2 sequence; B/DWI sequence, axial plane.
A. Small hyperintensive foci in the periventricular and subcortical white matter on both sides (arrowhead), with the right side dominating; one of these lesions is located in the left lateral geniculate body area - part of the visual tract (medium-sized arrow), another in the right occipital lobe (long arrow)
B. All lesions without signs of restricted diffusion (invisible on DWI images) – secondary vascular demyelination.
Source: own research

mentia. He underwent a psychiatric work-up, and he was diagnosed with the early stage of VaD, based on the DSM-5 diagnostic criteria [14]. All examinations, including laboratory tests, were performed as indicated to determine the etiology of the process.

The Rey-Osterrieth Complex Figure

In order to evaluate and compare certain specific dimensions of the patient's visuoconstructional deficits, we used the Rey-Osterrieth Complex Figure, with a new scoring system that divides the figure into six perceptual fields: right, left, upper, lower, basic gestalt, and inner detail. When the patient's results were compared with normal controls from the data base of the Brain Institute of the Polish Neuropsychological Society [6; see also 15], we found significant deficits in all six categories.

Neurophysiological examination

Also in 2018 he was assessed using the HBI methodology [see: 1,2,3,4,5,6], which consists in recording 19-channel EEG in resting state conditions, and again during a cued GO/NOGO task; the parameters of EEG spectra and ERPs were then compared with the normative and patient databases [2].

The cued GO/NOGO task

A variant of the cued GO/NOGO task was used to assess the brain correlates of cognitive control [2,3,4]. Images of two categories - animal (*a*) and plant (*p*) –

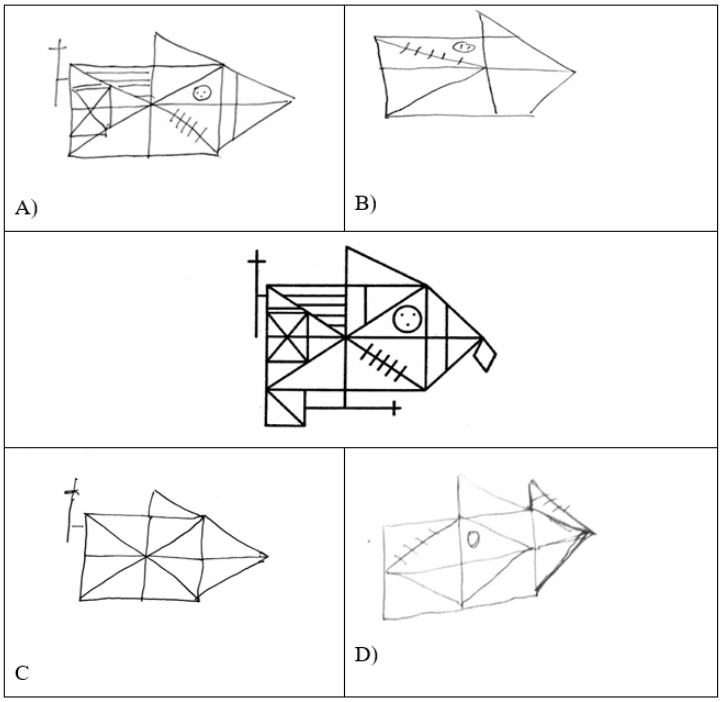

Fig. 3. Rey-Osterrieth Complex Figure (assessed with a new scoring system) as drawn by the patient in the first (A and B) and second examination (C and D). These results suggest that impaired performance on visuoconstructional tasks may result from left hemispatial inattention consequent to VaD. Source: own research

served as the relevant stimuli. The trials entailed the presentation of paired stimuli (*s1-s2*), using intervals of 1000 ms between stimuli and intervals of 3000 ms between trials. Four types of trials were presented: *a-a, a-p, p-p and p-h+novel sound,* where *h* means the image of a human. The duration of stimulus presentation was 100 ms. The subject was instructed to react to *a-a* trials (GO trials) by pressing the button under his right hand, and not to react to any other trials (NOGO trials).

The pictures were taken from children's schoolbooks, and edited to ensure that the overall luminance and image sizes of both animals and plants were approximately equal. To prevent habituation to repetitive stimuli, we presented twenty different animal images; plants and humans were randomly presented in various combinations. In order to encourage a certain level of alertness, novel sounds were occasionally presented in NOGO trials simultaneously with images of a human. These images accompanied by sound produced an orientation reaction in this patient, as indicated by the appearance of the P3 ERP wave, associated with novelty.

The trials were grouped into four blocks of 100 trials each. A unique set of five *a*, five *p*, and five *h* stimuli were set up for each block. Each of these blocks,

then, was presented in a pseudo-random order (with the same number of trials in all four categories) of 400 trials, 100 trials per category. The patient was encouraged to practice the task before we began the recording, and then rested for a few minutes after the halfway point (that is, after the first 200 trials). The patient was seated in an upright position, in a comfortable chair, with a clear view of the computer screen. The stimuli appeared on a 17-inch CRT computer screen placed 1.5 meters in front of the patient, and occupied 3.8° of his visual field.

Data recording

The patient's reactions to the trials were recorded in a separate channel. We calculated the mean and standard deviation for response latency. We also counted any errors of omission (failure to react to a GO trial) or commission (failure to suppress a reaction to a NOGO trial). The EEG was recorded at 19 scalp sites, using the 10-20-system, bandpass-filtered in the range between 0.3 and 50 Hz, and digitized at the rate of 250 samples per second per channel.

The EEG was recorded with reference to linked ears, allowing for re-montaging (that is, computational re-referencing of the data). The EEG was then re-referenced computationally to the common average montage. The recordings were made using a 19-channel PC-controlled EEG system, the "Mitsar-201" (CE 0537) manufactured by Mitsar, Ltd. The electrodes were attached to caps manufactured by Electro-Cap International, Inc. ECI ELECTRO-GEL was used to ensure that the recessed tin electrodes contacted the scalp. We used WinEEG software to collect the quantitative data [3].

Correction of artifacts

We corrected for eye blink artifacts by zeroing out the activation curves of specific independent components corresponding to eye blinks, which we identified by applying Independent Component Analysis (ICA) to the raw EEG fragments [2,17,18]. The method applied in the present study has been found to be comparable to an electrooculogram (EOG) regression technique, as described in Tereshchenko et al.[5]. In addition, epochs in which we detected excessive amplitude of filtered EEG, and/or excessive faster and/or slower frequency activity were automatically marked off and then excluded from further analysis. The exclusion thresholds were set as follows:

- for non-filtered EEG, 100 μV;
- for slow waves in the 0-1 Hz band, 50 μV;
- for fast waves filtered in the 20-35 Hz band, 35 μV [2].

RESULTS

Behavioral observations

Table 1 gives he parameters of the patient's performance in the cued GO/NOGO task in comparison to normative data. The normative data were collected from a group of healthy subjects (N=38) of similar age (52-58 years), whose data

Tab. 1. Behavioural data from the task
Source: own research

Comparision	Errors of omission	Errors of commission	Reaction time (RT)	SD
Patient	4	2	313	76
Norms	3.6	1.2	398	74
p-value	0.97	0.71	0.39	0.96

were available in the HBI database [1,2,6]. We found no statistically significant deviation from the reference values of any behavioral parameter.

Quantitative EEG

Figure 4 depicts the patient's EEG spectra deviations from the grand averaged spectra of the healthy control group (N=39). As one can see the patient's EEG is characterized by an enhanced alpha rhythm (with peak frequency at 8.3 Hz) at the posterior regions especially on the right side.

Event related potentials (ERPs).

Figure 5 shows the patient's ERPs in the cued GO/NOGO, as compared to the grand average ERP for 39 of healthy controls (HC). The amplitudes of the P3 GO and P3 NOGO waves in the patient are clearly larger (but not at the level of statistical significance) than those of the healthy controls. However, the latency of the P3 GO wave is significantly ($p<0.01$) delayed in comparison to the healthy

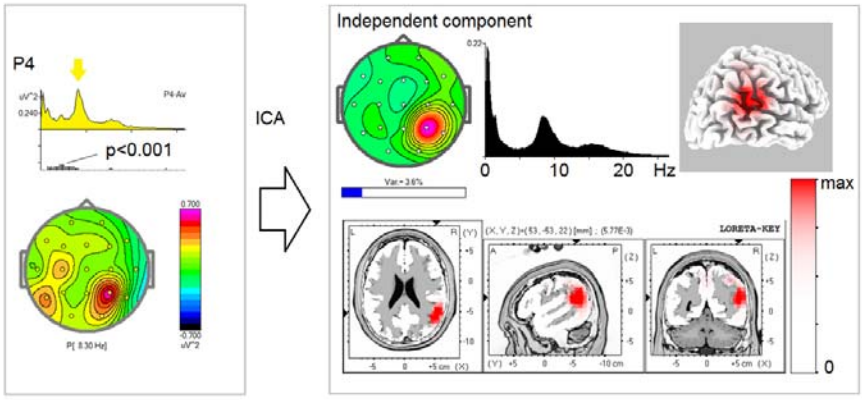

Fig. 4. EEG spectra in the cued GO/NOGO task in the patient in comparison to those of the healthy controls (N=39).
(a) Top: EEG spectra difference (the patient's results minus the grand average for the healthy controls) at P4, with indicators of the statistical significance of the diffidence below. Small vertical bars: $p<0.05$, large vertical bars: $p<0.001$. Bottom: map of spectra differences at the alpha frequency peak (indicated by arrow).
(b) Top: map, EEG spectra, and LORETA image of the independent component extracted from EEG in the task condition and corresponded to the main deviation from the reference. Bottom: LORETA 3-D current source densities the map above.
Source: own research

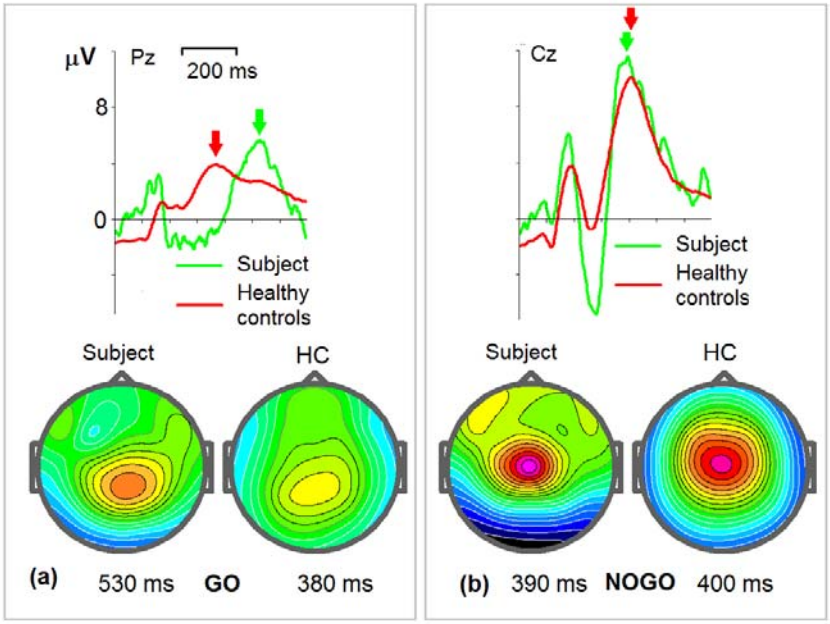

Fig. 5. ERPs in the cued GO/NOGO task in the patient in comparison to those of the healthy controls (N=39).
(a) Top: ERPs for GO trials recorded at Pz for the patient (green) and the healthy controls (red). Bottom: maps of the ERPs at the latency corresponding to the peak P3 GO waves recorded at Pz. (b) Top: for NOGO trials ERP recorded at Cz for the patient (green) and the healthy controls (red lines). Bottom: maps of the ERP at the latency corresponding to the peak P3 NOGO waves recorded at Cz.
Source: own research

controls (530 ms vs. 380 ms), whereas the latency of the P3 NOGO wave is nearly identical to the average for the healthy controls (390 ms vs. 400 ms).

Post-mortem finding

The patient died in 2019. Post-mortem studies confirmed cortical microhaemorrhages neuropathological criteria for VaD (Fig. 6). We did not found deposits of hyperphosphorylated tau (HPт) and Aβ, which fulfil the neuropathological criteria for AD.

Neuroimaging is indeed an important tool in the clinical diagnosis of CVLs and imaging-pathological correlative studies are aiming to bridge the gap between in vivo imaging and post-mortem neuropathology. However, general assumptions regarding the underlying pathogenesis of common in vivo MRI findings are not unequivocally corroborated by neuropathological findings and this may result in inadequate clinical diagnosis and treatment [22].

It should be pointed out that although most microbleed pathological correlation studies emphasise blood leakage from nearby damaged small vessels into the brain parenchyma as a mechanism, it must not be assumed that a primary haem-

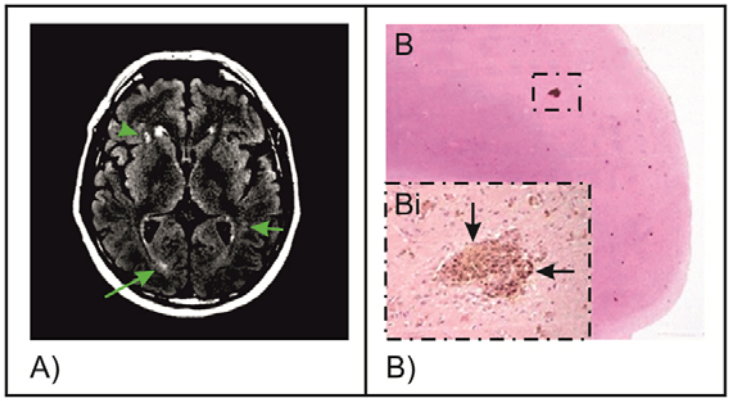

Fig. 6. Magnetic resonance imaging (MRI) and histological sections of cerebral tissue exhibiting microhaemorrhages from an 53-year-old man with dementia.
(A) radiological characteristics of microhaemorrhages inclusive of small, well-demarcated hypointense ovoid lesions (arrow). and severe cerebral amyloid angiopathy on pathology:
(B) magnified image of cortical microhaemorrhage; (Bi) increased magnified image of cortical microhaemorrhage – brown deposits are haemosiderin (arrow) and yellow deposit is haematoidin (arrow head), indicating the microhaemorrhage is subacute. Histological stain hematoxylin and eosin used on images B and bi. Scale bars represent 1000 μm in image B, and 100 μm in image Bi. Images prepared by Prof. Izabela Herman-Sucharska, MD., and Prof. Dariusz Adamek, MD.

orrhagic process fundamentally produces all microbleeds or that the most severely affected vessels are the culprits. Alternative non-haemorrhagic mechanisms for microbleeds, particularly if no tissue damage surrounds the vessel and haemosiderin is limited to the perivascular space, include ischaemia-mediated iron store release by oligodendrocytes [24], phagocytosis of red blood cell microemboli into the perivascular space (termed angiophagy) [25], or even haemorrhagic transformation of small microinfarcts [26].

It should be add, that a large proportion of patients with dementia who have significant CVLs also exhibit more severe concomitant AD pathology [22, 27]. We did not found deposits of hyperphosphorylated tau (HPт) and Aβ, which fulfil the neuropathological criteria for AD (Braak neurofibrillary tangle [NFT] stage V/VI, Consortium to Establish a Registry for Alzheimer's Disease [CERAD] score C and Aβ phase 5 according to the National Institute on Aging–Alzheimer's Association [NIA–AA] guidelines [28–31]). Therefore we did not classified the illness as mixed AD/VaD, but rather VaD.

DISCUSSION

The patient's performance in the cued GO/NOGO task was quite good, so that all behavioral parameters, (such as errors of omission or commission, reaction time and reaction time variability) did not deviate from the mean parameters of healthy controls at about the same age. Deviations from the reference values in EEG spectra indicate idling of the posterior regions of the patient's cortex, es-

pecially on the right side (alpha rhythms are idling rhythms of the brain) [1,2].

The amplitude and latency of the frontally-centrally distributed P3 NOGGO wave were within the normal limits, indicating intact operations of cognitive control in this patient [2,3,4,5,6]. The latency – but not the amplitude – of the parietally distributed P3 GO wave was statistically deviant from the normative data. This would be consistent with both the neuroimaging results, showing lesions in areas likely to affect visuo-constructive processing, and the results of the Rey-Osterrieth figure. The patient's inability to render the gestalt of the figures is also suggestive of right parietal dysfunction.

On the basis of these experimental data we can suggest that this patient has abnormalities in the posterior regions of the brain, consisting of hypofunctioning of the corresponding cortical areas and slowing of information processing in these areas. The slowing of information processing might be associated with a decrease of axonal conductivity in the posterior regions, which in turn might be caused by white matter lesions in these areas.

VaD can be extremely difficult to differentiate from other forms of dementia, including especially MCI (mild cognitive impairment) or DAT (dementia of the Alzheimer's type. Since it results from the accrued effects of numerous minor episodes, many of which produce no clinical symptoms at all and go unnoticed by the patient, the symptoms of VaD typically remain non-specific and subclinical. Thus the fact that, in the present study, only one neurophysiological parameter showed any deviation from the norm is hardly surprising in a patient with a history of TIAs. Rather than a single clearly visible cortical lesion affecting an easily delineated cortical region, as in the case of stroke patients, or a specific pattern of cortical and subcortical atrophy, as in a patient with, for example, DAT or frontotemporal dementia (FTD), the lesions that ultimately produce VaD are very small and widely, indeed randomly scattered around the brain. Indeed, it may be precisely the combination of an overall clinical picture suggesting something between MCI and early stage DAT with a lack of dramatic neuroimaging and/or neurophysiological results pointing to any of the more familiar etiologies of cognitive impairment might be precisely the distinguishing feature of VaD.

It is of course much too early to posit the specific result we obtained here - that is, the abnormal latency of the P3 GO wave - as a definitive neuromarker of VaD. More data is certainly needed. With a database of ERP results from patients with a similar clinical history, however, it may prove possible in the not-too-distant future to development an earlier and more empirically-based diagnosis of VaD, at considerably less expense (and conceivably greater accuracy) compared to, for example, MRI examinations [19]. Given the importance of early diagnosis in these cases, on the one hand, and the urgency of controlling spiraling health care costs in every country in the world [20, 21], this possibility seems to be worth exploring.

As this research continues, close cooperation will be essential between neuropsychologists, neurophysiologists, and other specialists involved in the investigation of the causes and effect of brain dysfunction. With an earlier, more precise,

evidence-based diagnosis, it may be possible to develop better, more focused clinical interventions for these patients, rather than purely palliative measures.

CONCLUSIONS

The patient studied here presented with a clinical history of TIAs and a neuropsychological picture suggestive of mild dementia. An analysis of the ERPs measured in a GO/NOGO task did not indicate more than a few obvious abnormalities, with the exception of increased latency in the P3 GO wave. All these factors, we have argued, lead to a diagnosis of vascular dementia.

With further research, ERPs in a GO/NOGO task can provide a powerful tool to assess functional brain abnormalities, in combination with clinical observation and neuropsychological testing. This may apply not only to VaD, but also to other dementia syndromes, the differential diagnosis of which remains inordinately difficult when based on a single modality.

REFERENCES

1. Bazanova OM, Vernon D. Interpreting EEG alpha activity. Neurosci Biobehav Rev. 2014 Jul; 44:94-110.
2. Kropotov JD. Functional neuromarkers for psychiatry. Application for diagnosis and treatment. Amsterdam, London, Paris, Sydney, Tokyo: Elsevier Academic Press; 2016.
3. Kropotov JD & Ponomarev VA. Decomposing N2 NOGO wave of event-related potentials into independent components. Neuroreport. 2009;20(18):1592-1596.
4. Kropotov JD, Ponomarev VA, Hollup S & Mueller A. Dissociating action inhibition, conflict monitoring and sensory mismatch into independent components of event related potentials in GO/NOGO task. NeuroImage. 2011;57:565-575.
5. Tereshchenko EP, Ponomarev VA, Kropotov I & Muller A. Comparative efficiencies of different methods for removing blink artifacts in analyzing quantitative electroencephalogram and event-related potentials. Fiziol Cheloveka. 2009;35(2):124-131.
6. Olearczyk E, Bogucki P, Sobieszak A. The EEG Split Alpha Peak: Phenomenological Origins and Methodological Aspects of Detection and Evaluation. Front. Neurosci., 12 September 2017. https://doi.org/10.3389/fnins.2017.00506
7. Degan D, Ornello R, Tiseo C, De Santis F, Pistoia F, Carolei A, Sacco S. Epidemiology of Transient Ischemic Attacks Using Time- or Tissue-Based Definitions: A Population-Based Study. Stroke. 2017;48:530–536. https://doi.org/10.1161/STROKEAHA.116.015417.
8. Li OL, Silver FL, Lichtman J, Fang J, Stamplecoski M, Wengle RS, et al.. Sex differences in the presentation, care, and outcomes of transient ischemicattack: resultsfrom the Ontario Stroke Registry. Stroke. 2016; 47:255–257. doi: 10.1161/STROKEAHA.115.010485.
9. Abbott Al, Silvestrini M, Topakian R, Golledge J, Brunser Am, de Borst GJ, Harbaugh RE, Doubal FN, Rundek T, Thapar A, Davies AH, Kam A, Wardlaw JM. Optimizing the Definitions of Stroke, Transient Ischemic Attack, and Infarction for Research and Application in Clinical Practice. Front. Neurol., 18 October 2017.| https://doi.org/10.3389/fneur.2017.00537
10. Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet (2015) 386:2145–91. doi:10.1016/S0140-6736(15)61340-X.
11. Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM. Prognostic value of “tissue-based” definitions of TIA and minor stroke. Neurology May 2019, 92 (21) e2455-e2461; DOI: 10.1212/WNL.0000000000007531.

12. Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, Russell RW, Symon L. Cerebral blood flow in dementia. Arch Neurol. 1975;32:632-637.
13. Prince M, Albanese E, Guerchet M, et al. World Alzheimer report 2014. Dementia and risk reduction: an analysis of protective and modifiable risk factors. Alzheimer's Disease International, 2014.
14. American Psychiatric Association: Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Washington, DC; 2013.
15. Taher M. Neurocognitive profile study of Parkinsonian patients by automatic analysis of Rey's Complex Figure. Acta Neuropsychologica 2019; 17: 437-443.
16. Robinson L, Tang E, Taylor JP. Dementia: timely diagnosis and early intervention. BMJ. 2015 Jun 16;350:h3029. doi: 10.1136/bmj.h3029. PMID: 26079686; PMCID: PMC4468575.
17. Makeig S, Jung T-P, Ghahremani D, Bell AJ, & Sejnowski TJ. Blind separation of event-related brain responses into independent components. Proceedings of the National Academy of Sciences of the United States of America. 1997;94:10979-10984.
18. Al Sawaf A, Murr N. EEG Basal Cortical Rhythms. [Updated 2019 Apr 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532986/
19. Jiang X, Bian GB, Tian Z. Removal of Artifacts from EEG Signals: A Review. Sensors (Basel). 2019 Feb 26;19(5):987. doi: 10.3390/s19050987. PMID: 30813520; PMCID: PMC6427454.
20 Kropotov JD. Functional neuromarkers for neuropsychology. Acta Neuropsychologica. 2018; 16(1):1-7.
21. Mazur A, Saran T, Łukasiewicz J, et al. Interpersonal correlates of the tendency to seek help in the situation of indebtedness in healthy people and in patients with impaired mobility, related to chronic disorders of the locomotor system – Pilot study. Annals of Agricultural and Environmental Medicine. 2019. doi:10.26444/aaem/102493.
22. Bermingham, SL. The appropriate use of neuroimaging in the diagnostic work-up of dementia: an economic literature review and cost-effectiveness analysis. Ont Health Technol Assess Ser. 2014;14(2):1–67.
23. McAleese, K. E., Alafuzoff, I., Charidimou, A., De Reuck, J., Grinberg, L. T., Hainsworth, A. H., Hortobagyi, T., Ince, P., Jellinger, K., Gao, J., Kalaria, R. N., Kovacs, G. G., Kövari, E., Love, S., Popovic, M., Skrobot, O., Taipa, R., Thal, D. R., Werring, D., Wharton, S. B., … Attems, J. (2016). Post-mortem assessment in vascular dementia: advances and aspirations. BMC medicine, 14(1), 129. https://doi.org/10.1186/s12916-016-0676-5.
24. Janaway BM, Simpson JE, Hoggard N, Highley JR, Forster G, Drew D, Gebril OH, Matthews FE, Brayne C, Wharton SB, et al. Brain haemosiderin in older people: pathological evidence for an ischaemic origin of magnetic resonance imaging (MRI) microbleeds. Neuropathol Appl Neurobiol. 2014;40(3):258–269. doi: 10.1111/nan.12062.
25. De Reuck J, Auger F, Cordonnier C, Deramecourt V, Durieux N, Pasquier F, Bordet R, Maurage CA, Leys D. Comparison of 7.0-T T(2)*-Magnetic Resonance Imaging of Cerebral Bleeds in Post-Mortem Brain Sections of Alzheimer Patients with Their Neuropathological Correlates. Cerebrovasc Dis. 2011;31(5):511–517. doi: 10.1159/000324391.
26. Grutzendler J, Murikinati S, Hiner B, Ji L, Lam CK, Yoo T, Gupta S, Hafler BP, Adelman RA, Yuan P, et al. Angiophagy prevents early embolus washout but recanalizes microvessels through embolus extravasation. Sci Transl Med. 2014;6(226):226ra231. doi: 10.1126/scitranslmed.3006585.
27. Korczyn AD. Mixed dementia—the most common cause of dementia. Ann N Y Acad Sci. 2002;977:129–134. doi: 10.1111/j.1749-6632.2002.tb04807.x.
28. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 2006;112(4):389–404. doi: 10.1007/s00401-006-0127-z.
29. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012;8(1):1–13. doi: 10.1016/j.jalz.2011.10.007.

30. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991;41(4):479–486. doi: 10.1212/WNL.41.4.479.
31. Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002;58(12):1791–1800. doi: 10.1212/WNL.58.12.1791.

Address for correspondence:
Prof. Maria Pachalska, PhD.
Chair of Neuropsychology and Neurorehabilitation
Andrzej Frycz Modrzewski Krakow University,
Andrzeja Herlinga-Grudzińskiego 1
30-750 Krakow, Poland
e-mail: neuropsychologia23@gmail.com