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Original Article

Neurophysiological evaluation of visual function in iRBD: potential role in stratifying RBD conversion risk

Michele Terzaghi [a, b, *], Alfredo Romani [c], Marina Ranzani [c], Roberto Callieco [c], Federica Avantaggiato [c], Riccardo Cremascoli [a, b], Marta Picascia [d], Laura Pilati [a, e], Dario Arnaldi [f, g], Valter Rustioni [a, b], Ivana Sartori [h], Roberta Zangaglia [i], Claudio Pacchetti [i], Silvia Colnaghi [c], Maurizio Versino [j]

[a] Unit of Sleep Medicine and Epilepsy, IRCCS Mondino Foundation, Pavia, Italy
[b] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[c] Laboratory of Evoked Potentials, IRCCS Mondino Foundation, Pavia, Italy
[d] Laboratory of Neuropsychology/Alzheimer's Disease Assessment Unit, IRCCS Mondino Foundation, Pavia, Italy
[e] Department of Biomedicine and Clinical Neuroscience, University of Palermo, Italy
[f] Clinical Neurology, DINOGMI, University of Genoa, Genoa, Italy
[g] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[h] C. Munari Center of Epilepsy Surgery, Niguarda Hospital, Milan, Italy
[i] Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy
[j] Neurology and Stroke Unit, ASST Sette Laghi Ospedale di Circolo, Varese; DMC University of Insubria, Varese, Italy

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ABSTRACT

Study objectives: To evaluate neurophysiological alterations of visual function in idiopathic REM sleep Behavior Disorder (iRBD) both as markers and predictors of neurodegenerative disorders.
Methods: In a longitudinal follow-up study of 46 consecutive iRBD patients (follow-up duration 8.4 ± 3.4 years), the baseline parameters in luminance-contrast pattern (VEPp), red-green color (VEPc) and motion-onset (VEPm) Visual Evoked Potentials in iRBD were compared to early (ePD) and advanced (aPD) Parkinson's Disease subjects. Parameters of latency and amplitude of iRBD converters to neurodegenerative disease were compared with those of the non-converters.
Results: The VEP P100 mean latency values for both eyes and for both stimulation checks (30′ and 15') were significantly longer in all the three groups of patients as compared to controls; moreover latencies were longer in aPD than in the iRBD group who did not differ from the ePD group. The same held true when we analyzed the number of abnormal subjects belonging to each diagnostic group with a higher number of abnormal subjects in the aPD group compared to both the ePD and in iRBD groups. Chromatic and motion potentials were not different from controls and did not differ in the 3 diagnostic groups. The iRBD subjects who converted to a neurodegenerative disorder showed longer P100 latencies and a higher occurrence of VEPp abnormalities than those who did not convert. Again chromatic and motion VEPs were not different depending on conversion.
Conclusions: In iRBD patients the detection of an abnormal VEPp should be considered as a red flag for possible synnucleinopathy, eventually contributing in stratifying the risk of phenoconversion.

1. Introduction

REM sleep behavior disorder (RBD) is a condition characterized by complex and often violent behaviors during sleep. Isolated RBD (iRBD) has a prevalence of 0.74–1.15% in those over 60 [1,2]. Most patients with iRBD develop a neurodegenerative disease and this risk increases over time: 17.9%–25% at 3 years, rising to 31–41% at 5 years [3,4], 60% at 10 years and 73% at 12 years [4] according to multicentric studies. Therefore, RBD has a strong association with neurodegenerative diseases.

Identification of novel biomarkers in RBD that reflect the presence of an impending neurodegeneration still represents a critical

* Corresponding author. Sleep Medicine and Epilepsy Unit, IRCCS Mondino Foundation, Via Mondino, 27100 Pavia, Italy. Fax: +390382380286.
E-mail address: michele.terzaghi@mondino.it (M. Terzaghi).

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issue in RBD and, furthermore, current research is struggling to stratify RBD subjects with respect to their risk of early phenoconversion to parkinsonism or dementia.

Among early biomarkers that reflect the presence and progression of a neurodegenerative process, visual function in RBD was studied in the form of color vision. Color vision impairment was found in patients with iRBD and RBD in PD [5,6].

Adjusting for age and sex, colour vision significantly predicted the risk of dementia and parkinsonism (HR = 1.69). When comparing patients with and without color vision abnormalities in iRBD, the Kaplan–Meier disease-free survival was about 55% versus 70% at 4 years and 20% versus 55% at 7 years [4]. Among iRBD subjects who develop Lewy Body disease, color vision anomalies predicted the early onset of dementia with respect to parkinsonism [4].

Visual evoked potential is a noninvasive widely used technique for studying the neural conductive activity of the visual pathway. Despite its practicability, it has not yet been routinely used by research groups in the present context. Indeed, no studies so far studied visual abnormalities in iRBD using neurophysiological methods.

The aim of this study, that includes cross sectional and longitudinal evaluations, was to study the utility of neurophysiological assessment of visual function as marker of the disease and its ability to predict the evolution to PD/dementia by using different electrophysiological techniques, ie luminance-contrast pattern VEPs (VEPp), red-green color VEPs (VEPc) and motion-onset VEPs (VEPm), in iRBD compared to early- and advanced-PD subjects.

2. Methods

2.1. Subjects

46 consecutive iRBD subjects (43 males; mean age 68.3 ± 6.3 years, disease duration 10.6 ± 6.7 years; UPDRS part III: 4.4 ± 5.4; MMSE 28.1 ± 2.9, abnormal DAT scan in 28.3%) diagnosed according to the International Classification of Sleep Disorders second or third edition underwent luminance-contrast VEPs, red-green color VEPs and motion-onset VEPS. Minimum duration of clinical follow up was 12 months (mean follow-up duration 7.79 ± 4.21 years). The local institutional review board approved the study and all subjects gave their informed consent prior to their inclusion.

Clinical, neurological and neuropsychological evaluations were performed at baseline and at regular follow-up visits: clinical evaluation included MDS-UPDRS-III to detect subtle motor symptoms and Mini-Mental state examination (MMSE) as a marker of global cognition.

Exclusion criteria were abnormal best-corrected visual acuity, diagnosis of any ophthalmological disease or subjective report of impaired vision, presence of overt neurodegenerative disease or dementia, any neurological comorbidity, post-traumatic stress disorder, substance or alcohol abuse. All subjects stopped clonazepam and/or melatonin at least 7 days before performing visual evoked potentials.

2.2. Follow-up and disease conversion

Both at baseline and follow-up, dementia was defined as a cognitive decline from a previous level of performance sufficient to interfere with independence, and resulting in the patients themselves, or their relatives, reporting impairment in any activity of daily living when administered the Instrumental Activities of Daily Living (IADL) scale [7]. Each patient with suspected dementia underwent a comprehensive neuropsychological assessment performed by an experienced neuropsychologist. MCI (present in 15.2% of iRBD subjects) was not considered sign of phenoconversion [8].

iRBD subjects were prospectively followed with in-person evaluation to diagnose phenoconversion to parkinsonism (diagnosed according to the MDS clinical diagnostic criteria for Parkinson's disease) [9], dementia with Lewy bodies (according to DLB Consortium guidelines [10] by consensus between a neurologist and a neuropsychologist), multiple system atrophy (MSA) according to consensus criteria [11].

2.3. Comparison subjects

59 subjects affected by idiopathic Parkinson's Disease served as comparison group: all the patients were on L-DOPA treatment, nine of them in association with dopamine agonists early-stage PD: 32 subjects (20 males; mean age 62.6 ± 11.5 years, disease duration 0.8 ± 0.8 years; UPDRS part III: 12.3 ± 7.2; MMSE 27.1 ± 3.2, 2 on dopamine agonists; Levo DOPA equivalent daily dose: 121.1 ± 126.8) with diagnosis of Idiopathic Parkinson's Disease [9] and less than two years since symptom onset, no motor fluctuations at the time of examination, no overt cognitive impairment, confirmed dopaminergic presynaptic dysfunction on DAT SCAN advanced-stage PD: 27 subjects with diagnosis of IPD and motor fluctuations or at least 5 years since symptom onset (16 males; mean age 71.3 ± 7.2 years, disease duration 7.8 ± 4.7 years; UPDRS part III: 29.5 ± 11.2; MMSE 26.2 ± 3.5, 7 on dopamine agonists; Levo DOPA equivalent daily dose: 880.8 ± 494.8). For subjects with motor fluctuations, VEPs were performed in “ON” condition.

2.4. Visual evoked potentials (VEPs)

Visual evoked potentials were recorded and analyzed by a Mizar-Sirius device equipped with two dedicated softwares (Galileo NT and Basic BE). The visual stimuli were generated by MatLab version 7.3.0 (R2006b).

All VEPs were recorded after monocular stimulation using Ag/AgCl superficial cup electrodes, 10 mm in diameter, placed accordingly to the 10–20 international system in Oz (active), Cz (reference) and at the ear lobe (ground). Signals were amplified (50,000 fold), bandpass filtered between 1 and 100 Hz (12 and 6 dB octave), digitized at 2 kHz with 12-bit resolution, and averaged online. Time base was 300 ms for standard VEPs, 500 ms for color and motion VEPs.

For ‘standard’ pattern reversal visual evoked potentials (VEPp) we used a luminance checkerboard stimulation mean luminance 50 cd/m2; contrast 100%, check sizes were 30′ and 15′, and 2 series of 100 artifact-free responses were averaged for each check and each eye.

For red-green (R-G) visual evoked potentials (VEPc) we referred to Sartucci et al. [12]:color visual stimuli were R-G equiluminant horizontal sinusoidal gratings of 2 c/deg presented in the central circular portion of the screen subtending 12 deg when viewed from 100 cm. R-G chromatic gratings were obtained by superimposing (out of phase by 180°) red– black to green– black luminance gratings, with the same Michelson contrast (90%), which was used to define the contrast of the chromatic gratings; they were presented for 300 msec (onset) and removed (contrast set to zero) for 700 msec (offset). 2 series of 80–100 artifact free responses to onset were averaged. Sweeps containing signals higher than 42 microV were rejected automatically.

Motion-onset VEPs (VEPm) were obtained according to Kuba et al. [13] with a radial motion paradigm. The stimulus consisted of a 22° circular field containg concentric rings with a radial sinusoidal luminance profile (mean luminance 10 cd/m2; 10% Michelson contrast). The frequency of the sinusoidal profile increased from 0.2 cpd at 11° (outer border) to 0.6 cpd at 2,5°. The 5° diameter central part had a uniform luminance corresponding to the mean luminance. The motion-onset effect was achieved by varying the

phase of the sinusioid obtaining an expansion of the rings. The speed of the movement was set at 5 Hz and, given the increase of the spatial frequency of the sinusoids towards the periphery, the angular velocity increased in the inner to the outer border. The duration of the movement was set at 200 ms. This was followed by a 1250 ms interval with a unmoving stimulus. Stimulation was performed in blocks of 30 pairs of stimuli. The recording parameters were the same as for the R-G VEPs. Two series of 60–70 artifact-free responses to motion onset were averaged.

We considered the following parameters:

1) For the pattern reversal visual evoked potentials the peak latency (L) of P100 component and the N70–P100 peak-to-peak amplitude (A)
2) For the red-green chromatic visual evoked potentials the peak latency and the baseline-to peak amplitude of the N1 component
3) For the motion visual evoked potentials the peak latency and the baseline-to-peak amplitude of the N2 component

2.5. Statistical analysis

We considered separately the responses obtained from the two eyes, and we rated them as abnormal if they were missing or not reliable, or if their values were either larger (for the latencies) or smaller (for the amplitudes) than the normal limits computed in our laboratory. For each subject we acknowledged the occurrence of an abnormality when at least one eye proved to be abnormal.

The Kolmogorov Smirnov test proved that the distribution of the values of all of our variable was not different from the normal distribution. We compared the mean values of each parameter from each group of patients with the database of control subjects used to compute the normal values of our laboratory that takes into account the age when this is proven to be a significant factor. More specifically, we transformed the value from each subject in the corresponding z-score and, for each group of patients, we tested if the mean value of the z-scores significantly differed from zero in a t distribution.

We compared the mean values from the different groups by analyses of variance, and we performed the Scheffèe test as a post-hoc test to pinpoint significant differences (or similarities) between pairs of groups. Since the mean age of the 3 groups of patients proved to be statistically significant ($F = 6.75$, $p = 0.002$) we introduced age as a covariate in the analyses of variance. The age factor as a covariate proved to be statistically significant for all the latencies but for none of the amplitudes that we considered. Accordingly, the analyses were performed on residuals rather than on the raw data.

We compared the number of abnormal responses detectable in the three groups of patients by chi-square test (or Fishers's exact test). [In case of a significant value, we made additional chi-square tests to compare pairs of group of patients].

The correlation analyses were based on the computation of Pearson's correlation coefficient.

In the RBD group we compared the mean values and the number of abnormalities by considering the possible conversion to a different diagnosis (PD and/or cognitive dysfunction); accordingly, we identified 2 subgroups belonging to the RBD group: not converters, converters.

3. Results

Latency and amplitude raw values and number of subjects with pathological values compared to laboratory controls are reported in Tables 1 and 2.

For pattern reversal visual evoked potentials, in the iRBD group the z-scores computed for the latencies proved to be significantly longer than in controls for both eyes and for both checks (left eye: 30′ checks $p = 0.021$ - 15′ checks $p = 0.0231$; right eye 30′ checks $p = 0.016$ - 15' checks $p = 0.004$).

The same occurred for early PD group (left eye 30′ checks $p = 0.036$ - 15′ checks $p = 0.021$; right eye 30′ checks $p = 0.018$- 15′ checks $p = 0.0026$) and advanced PD group (left eye 30′ checks $p = 0.001$–15′ checks $p = 0.001$; right eye 30′ checks $p = 0.0001$–15' checks $p = 0.001$).

When we compared the 3 groups of patients, the P100 latency in both eyes and for both checks proved to be statistically different. The Scheffè test suggested that these differences were mainly attributable to the advanced PD group and the iRBD groups, while no statistical differences were found between the early PD and the iRBD group (*p* values are reported in Table 1). The number of subjects with a pathological P100 latency proved to be significantly different, and the PD-advanced group showed a higher occurrence of abnormalities than the other two-groups for both eyes and with both checks (Table 2).

For chromatic and motion visual evoked potential none of the z-scores in any of the 3 groups proved to be statistically different from controls; the percentage of subjects with abnormalities in chromatic or motion visual evoked potentials was not different in the 3 groups of patients.

Examples of normal and pathological VEPs are shown in Fig. 1.

3.1. Clinical, sleep related and VEPs' parameters

We looked for possible relationship between clinical (disease duration, MMSE score, UPDRS part III score) and sleep macrostructure parameters (total sleep time, sleep latency, REM latency, wake after sleep onset, percentage of phase 1N, 2N, 3N and REM, sleep efficiency, Periodic Limb Movement index and REM Atonia Index) and the VEP parameters.

None of these parameters were significantly correlated to any of the VEP parameters.

3.2. Follow up results in the iRBD group

Fifteen (32.1%) subjects converted to a neurodegenerative disorder: 13 to parkinsonism (12 PD and 1 MSA) and 3 to dementia (probable DLB). They showed a mean latency to conversion of 8.4 ± 3.4 years.

As compared to not converters, converters showed a longer P100 latency with 30' (left eye $p = 0.035$; right eye $p = 0.029$) and 15' check (left eye $p = 0.01$; right eye $p = 0.034$).

For the same parameter we found an higher occurrence of abnormalities among the patients who converted at 15' check: left eye 38.9% versus 0% ($p = 0.001$) and right eye 38.9% versus 7.1% ($p = 0.012$).

In an additional analysis we checked if there was a correlation between VEP and the most affected body side without finding any significant correlation.

4. Discussion

iRBD is the biomarker with by far the strongest association with neurodegenerative diseases.

Within iRBD, other biomarkers were studied in order to identify in advance subjects with risk of early phenoconversion. Such clinical markers include clinical and neurophysiological markers [14], among which alterations of visual system, in the form of impaired color vision by clinical testing.

Table 1
Visual Evoked Potentials parametres in the three groups of subjects. LE: Left Eye; RE: Right Eye; VEP: Visual Evoked Potentials.

	RBD (n = 46) mean ± sd	Early PD (n = 32) mean ± sd	Advanced PD (n = 27) mean ± sd	*F; p*	*Pairwise comparisons (p in Scheffe test)*
30′ checks VEPs					
P100 latency LE	112.1 ± 8.0	110.4 ± 6.7	119.06 ± 11.9	*3.25; 0.043*	*Advanced PD vs RBD (0.05)*
P100 latency RE	113.1 ± 7.8	111.7 ± 10.0	122.29 ± 10.9	*3.33; 0.027*	*Advanced PD vs RBD (0.03)*
P100 amplitude LE	6.53 ± 2.68	7.87 ± 4.26	7.31 ± 3.0		
P100 amplitude RE	6.12 ± 2.72	7.09 ± 3.97	7.02 ± 2.71		
15′ checks VEPs					
P100 latency LE	120.5 ± 8.6	119.9 ± 13.0	132.98 ± 15.2	*4.46; 0.012*	*Advanced PD vs RBD (0.01)*
P100 latency RE	123.3 ± 8.4	121.6 ± 17.0	134.7 ± 17.2	*3.27; 0.041*	*Advanced PD vs RBD (0.05)*
P100 amplitude LE	7.24 ± 2.7	8.34 ± 4.60	7.57 ± 3.68		
P100 amplitude RE	7.18 ± 3.06	8.13 ± 4.54	7.17 ± 3.48		
Chromatic VEPs					
N1 latency LE	150.8 ± 25.0 (45)	149.6 ± 33.5 (30)	152.6 ± 18.8 (24)		
N1 latency RE	150.4 ± 23.0 (44)	152.7 ± 35.6 (29)	157.0 ± 29.5 (23)		
N1 amplitude LE	5.13 ± 2.78 (45)	4.51 ± 3.53 (30)	5.51 ± 3.08 (24)		
N1 amplitude RE	4.56 ± 2.64 (44)	4.72 ± 3.55 (29)	5.43 ± 3.63 (23)		
Motion VEPs					
N2 latency LE	180.5 ± 19.2 (45)	171.4 ± 18.4 (30)	183.7 ± 14.6 (25)		
N2 latency RE	179.6 ± 19.8 (45)	171.0 ± 17.9 (30)	186.0 ± 17.9 (26)		
N2 amplitude LE	5.63 ± 2.33 (45)	6.41 ± 3.47 (30)	6.76 ± 3.8 (25)		
N2 amplitude RE	5.51 ± 2.59 (45)	6.33 ± 3.0 (30)	6.62 ± 2.42 (26)		

Table 2
Percentage of subjects with pathological Visual Evoked Potentials (VEPs), LE: Left Eye; RE: Right Eye.

	RBD % (n = 46)	Early PD % (n = 32)	Advanced PD % (n = 27)	Chi-square/Fisher's exact test; *p*	*Pairwise comparisons*
30′ checks VEPs					
P100 latency LE	23.9	15.6	61.5	16.1; 0.0001	Advanced PD vs RBD and Early PD
P100 latency RE	34.8	28.1	65.4	9.35; 0.009	Advanced PD vs RBD and Early PD
P100 amplitude LE	10.9	9.4	11.5		
P100 amplitude RE	13	18.8	23.1		
15′ checks VEPs					
P100 latency LE	15.2	31.3	51.9	11.4; 0.004	Advanced PD vs RBD and Early PD
P100 latency RE	19.6	31.3	59.3	12.1; 0.002	Advanced PD vs RBD and Early PD
P100 amplitude LE	4.3	12.5	25.9		
P100 amplitude RE	6.5	9.4	14.8		
Chromatic VEP					
N1 latency LE	30.4	46.9	25.9		
N1 latency RE	26.1	46.6	33.3		
N1 amplitude LE	8.7	21.9	11.1		
N1 amplitude RE	10.9	18.8	11.1		
Motion VEP					
N2 latency LE	6.3	6.5	3.7		
N2 latency RE	6.5	3.1	11.1		
N2 amplitude LE	4.3	6.3	3.7		
N2 amplitude RE	6.5	3.1	3.7		

Visual dysfunction is common in PD, including abnormal contrast sensitivity, motion perception abnormalities, and color vision [12,15]. Parkinson's disease is characterized by loss of retinal ganglion cells as part of the neurodegenerative process and optical coherence tomography demonstrated optic atrophy [16]. The presence of α-synuclein deposition was demonstrated in the retina of PD patients [15]. Retinal thinning is documented in the early stages of PD and correlates with nigral cells loss [17].

Visual pathways include two main parallel streams, the parvocellular path, crucial for analyzing the details of the object and the analysis of color, and the magnocellular path, crucial for the analysis of movement and spatial relationships between objects [18]. The parvocellular pathway includes a inter-blob path specialized for analysis of the forms that is crucial for analyzing the details of the objects and to a limited extent of the colors, and a color sensitive path via blob regions sensitive to different wavelengths [18]. The parvocellular cells are more vulnerable in PD and the foveal area is featured by a remodeling as consequence of the neurodegeneration [19], as shown also by the interocular asymmetry for the foveal thickness [20].

We checked the utility of neurophysiological evaluation of the visual system by exploring standard pattern reversal VEPs, chromatic and motion VEPs, exploring more selectively the parvo- and the magnocellular paths.

Our results showed an increase in the latency of pattern VEPp in iRBD, but not alterations in their amplitude, similar to what occurs in subjects with early PD. With advancing of Parkinson's disease, latency of VEPp further increases. This has already been described for Parkinson's Disease [21] with studies reporting functional changes to be correlated with disease duration and severity of PD [22]. Therefore, altered VEPp represent a marker of neurodegeneration and VEPp are candidate to be a useful tool to follow neurodegeneration progression and potentially the effect of neuroprotective drugs, once available. Furthermore, latency of VEPp 15′ checks proved to distinguish iRBD subjects who developed early a neurodegenerative disorder from those who did not convert. Hence,

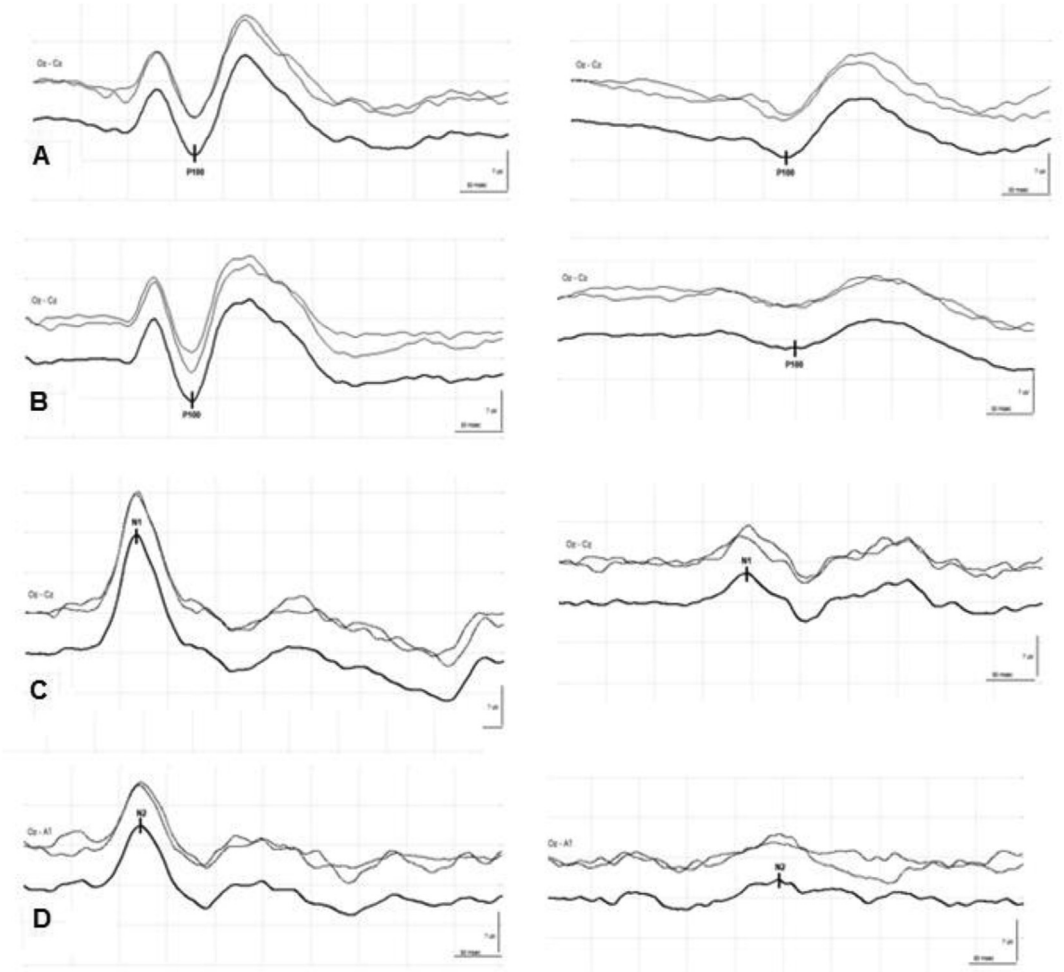

Fig. 1. Examples of normal (left column) and pathological (right column) VEPs (single traces - thin lines, and grand average - thick line). A: VEPp 30′ checks; B: VEPp 15′ checks; C: VEPc; D: VEPm.

VEPp exploring the foveal, mostly parvocellular path can represent an additional biomarker to outline the risk of phenoconversion.

Despite this result, our VEP paradigms more focused on the parvo- (15′ checks VEPp and VEPc) or magnocellular (30' checks VEPp and VEPm) pathways were not able to highlight a different or selective involvement of one of these two pathways as marker of state.

The report of structural involvement of parvocellular-related functions and structures [20,23] led to the use of color-contrast VEPs [24,25], which reportedly should be more sensitive in reflecting the underlying state of degeneration. Chromatic VEPs are a specific tool to explore parvocellular pathway integrity. Despite the theoretical basis, in our cohort the red-green chromatic VEP proved useless for marking neurodegeneration or for quantifying and following the evolution of damage in iRBD. Chromatic VEPs to blue-yellow stimuli elicit a different response than VEPs to red-green stimuli [24,26,27], so that a change in the stimulation paradigm should be evaluated to improve the diagnostic potentiality of chromatic VEP in iRBD and PD.

Motion perception is mediated by the magnocellular pathway. Cortical cells of the magnocellular pathway receive inputs from ganglionic cells and have aligned receptive fields selective for direction (ie are stimulated when the stimulus moves in a specific direction). Neurons that show this selectivity are crucial for analyzing the movement of objects. Despite motion perception is reportedly to be altered in PD [14,15], motion VEPs in our study show pathological results in a very small percentage of iRBD and PD subjects. Thus, this way to evaluate the magnocellular pathway seems useless in iRBD, both as a marker of status and as an indicator of evolution.

Changes in VEPs reflect the functional and structural integrity of the whole visual pathway, from retina to associative cortices. As such, VEPs alterations do not give insights to a better understanding of the pathophysiology of visual alterations in iRBD. Dopamine is widely represented in the retina, lateral geniculate body and visual cortex [21], therefore changes VEPs in iRBD as well as in PD might be due to the deficit in dopaminergic transmission in the retina and the central nervous system. Although the role of retinal dopaminergic dyfunction seems certain in determining VEP abnormalities [24,28], the involvement of visual as well as associative brain areas is also hypothesized on the basis of abnormal orientation sensitivity [29] or depth perception [30]. Indeed, it has been hypothesized that nondopaminergic alterations in visual processing affect the visual responses [21].

Retina thickness has been described in iRBD as a marker of neurodegeneration [31]. In our study data from optical coherence tomography are only available for a small percentage of subjects, thus correlation of retinal thickness and VEPs cannot be performed. This possible relationship should be investigated in future studies.

In consideration of the low cost, high tolerability, non-invasiveness and easily availability, neurophysiological evaluation of visual function can be usefully used to study neurodegeneration in iRBD, providing indications on its presence and potentially following its evolution.

Statement of significance

We checked the utility of neurophysiological evaluation of the visual system by exploring standard pattern reversal (VEPp), chromatic (VEPc) and motion Visual Evoked Potentials (VEPs). Our results showed an increase in the latency of pattern VEPp in iRBD similar to what occurs in subjects with early PD. P100 latencies were longer and occurrence of VEPp abnormalities were higher in iRBD subjects who converted to a neurodegenerative disorder. In consideration of the low cost, high tolerability, non-invasiveness and easily availability, VEPp can be usefully used as marker of status and as an indicator of possible evolution in iRBD.

Credit author statement

Dr Michele Terzaghi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization.

Dr Alfredo Romani: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing.

Dr Marina Ranzani: Investigation, Data Curation.

Dr Roberto Callieco: Investigation, Resources.

Dr Federica Avantaggiato: Data Curation.

Dr Riccardo Cremascoli: Investigation, Data Curation.

Dr. Marta Picascia: Investigation, Data Curation.

Dr. Laura Pilati: Data Curation.

Dr Dario Arnaldi: Writing - Original Draft.

Dr Valter Rustioni: Investigation, Resources.

Dr. Ivana Sartori: Writing - Review & Editing.

Dr. Roberta Zangaglia: Investigation, Data Curation.

Dr. Claudio Pacchetti: Investigation, Data Curation.

Dr Silvia Colnaghi: Methodology.

Dr Maurizio Versino: Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization.

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.05.006.

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