14. Ntanasi E, Maraki M, Yannakoulia M, et al. Frailty and prodromal Parkinson’s disease: results from the HELIAD study. J Gerontol A Biol Sci Med Sci 2021;76(4):622–629. https://doi.org/10.1093/gerona/glaa191
15. Charisis S, Ntanasi E, Yannakoulia M, et al. Mediterranean diet and risk for dementia and cognitive decline in a Mediterranean population. J Am Geriatr Soc 2021;69(6):1548–1559. https://doi.org/10.1111/jgs.17072
16. Bougea A, Maraki MI, Yannakoulia M, et al. Higher probability of prodromal Parkinson’s disease is related to lower cognitive performance. Neurology 2019;92(19):e2261–e2272. https://doi.org/10.1212/wnl.0000000000007451
17. Maraki MI, Yannakoulia M, Stamelou M, et al. Mediterranean diet adherence is related to reduced probability of prodromal Parkinson’s disease. Mov Disord 2019;34(1):48–57. https://doi.org/10.1002/mds.27489
18. Giagkou N, Maraki MI, Yannakoulia M, et al. A prospective validation of the updated movement disorders society research criteria for prodromal Parkinson’s disease. Mov Disord 2020;35(10):1802–1809. https://doi.org/10.1002/mds.28145
19. Maraki MI, Stefanis I, Yannakoulia M, et al. Motor function and the probability of prodromal Parkinson’s disease in older adults. Mov Disord 2019;34(9):1345–1353. https://doi.org/10.1002/mds.27792
20. Mahlknecht P, Gasperi A, Williet P, et al. Prodromal Parkinson’s disease as defined per MDS research criteria in the general elderly community. Mov Disord 2016;31(9):1405–1408. https://doi.org/10.1002/mds.26674
21. Charisis S, Ntanasi E, Yannakoulia M, et al. Plasma GSH levels and Alzheimer’s disease. A prospective approach: results from the HELIAD study. Free Radic Biol Med 2021;162:274–282. https://doi.org/10.1016/j.freeradbiomed.2020.10.027
22. Look MP, Rockstroh JK, Rao GS, et al. Serum selenium, plasma glutathione (GSH) and erythrocyte glutathione peroxidase (GSH-Px) levels in asymptomatic versus symptomatic human immunodeficiency virus-1 (HIV-1)-infection. Eur J Clin Nutr 1997;51(4):266–272. https://doi.org/10.1038/sj.ejcn.1600401
23. Campolo J, De Maria R, Cozzi L, et al. Antioxidant and inflammatory biomarkers for the identification of prodromal Parkinson’s disease. J Neurol Sci 2016;370:167–172. https://doi.org/10.1016/j.jns.2016.09.050
24. Iacono D, Geraci-Erck M, Rabin ML, et al. Parkinson disease and incidental Lewy body disease: just a question of time? Neurology 2015;85(19):1670–1679. https://doi.org/10.1212/wnl.0000000000002102
25. Califf RM. Biomarker development: lessons from the HELIAD study. Free Radic Biol Med 2021;162:274–282. https://doi.org/10.1016/j.freeradbiomed.2020.10.027
26. Wu G, Fang Y-Z, Yang S, Lupton JR, Turner ND. Blood and plasma glutathione measured in healthy subjects by HPLC: relation to sex, aging, biological variables, and life habits. Clin Chem 1995;41:1509–1517. https://doi.org/10.1093/clinchem/41.10.1509
27. Flagg EW, Coates RJ, Jones DP, et al. Plasma total glutathione in humans and its association with demographic and health-related factors. Br J Nutr 1993;70(3):797–808. https://doi.org/10.1079/bjn19930175
28. Blanco RA, Ziegler TR, Carlson BA, et al. Diurnal variation in glutathione and cysteine redox states in human plasma. Am J Clin Nutr 2007;86(4):1016–1023. https://doi.org/10.1093/ajcn/86.4.1016

Supporting Data
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Chromatic Pupillometry in Isolated Rapid Eye Movement Sleep Behavior Disorder

Chiara La Morgia, MD, PhD1,2 Martina Romagnoli, PhD,1 Fabio Pizza, MD, PhD2,3
Francesco Biscarini, MD,2 Marco Filardi, PhD,2,3,4 Vincenzo Donadio, MD, PhD,1,5 Michele Carbonelli, MD,2 Giulia Amore, MD,2 Jason C. Park, PhD,5 Michele Tinazzi, MD, PhD,6 Valerio Carelli, MD, PhD,1,2 Rocco Lugliari, MD, PhD,1,2 Giuseppe Plazzi, MD, PhD,1,2 and Elena Antelmi, MD, PhD6

1. IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy 2. Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy 3. Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari “Aldo Moro”, Bari, Italy 4. Center for Neurodegenerative Diseases and the Aging Brain, University of Bari “Aldo Moro”- A.O. Pia Fondazione Cardinale G. Panico, Tricase, Italy 5. Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois, USA 6. Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona, Verona, Italy 7. Department of Biomedical, Metabolic and Neurosciences, University of Modena and Reggio Emilia, Modena, Italy

ABSTRACT: Background: Melanopsin retinal ganglion cell (mRGC)-mediated pupillary light reflex (PLR) abnormalities have been documented in several neurodegenerative disorders including Parkinson’s disease. Overall, isolated rapid eye movement (REM) sleep behavior disorder (IRBD) represents the strongest prodromal risk factor for impending α-synucleinopathies.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Correspondence to: Dr. Chiara La Morgia, IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Via Altura 3, 40139, Bologna, Italy. E-mail: chiara.lamorgia@unib.it

Chiara La Morgia and Martina Romagnoli equally contributed to the manuscript.

Giuseppe Plazzi and Elena Antelmi equally contributed to the manuscript.

Relevant conflicts of interest/financial disclosures: The authors declare that they have no conflict of interest related to the research covered in this article.

Funding agency: This work was supported by GR-2013-02358026 Italian Ministry of Health grant to Chiara La Morgia.

Received: 15 May 2021; Revised: 1 August 2021; Accepted: 10 September 2021

Published online 7 October 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28809
Melanopsin retinal ganglion cells (mRGCs) are intrinsically photosensitive RGCs due to their expression of the photopigment melanopsin, modulating non-image forming functions of the eye such as circadian photoentrainment and pupillary light reflex (PLR), via projections to the hypothalamic suprachiasmatic and olivary pretectal nuclei, respectively. In vivo exploration of mRGC function is difficult since these cells represent a small RGC subgroup (about 1%) receiving inputs from rods and cones.

Considering that mRGCs are maximally sensitive to blue light at 480 nm, chromatic pupillometry protocols have been developed to isolate the mRGC contribution to the PLR relying on light stimuli at different wavelengths. Previous studies documented the presence of PLR abnormalities and mRGC dysfunction as well as mRGC loss in post-mortem retinas of patients with Parkinson’s disease (PD) and altered pupil behavior has been recently described also in idiopathic/isolated rapid eye movement (REM) sleep behavior disorder.

Idiopathic/isolated rapid eye movement (REM) sleep behavior disorder (iRBD) represents the strongest prodromal risk factor for α-synucleinopathies. The presence of nigrostriatal dopaminergic denervation, motor symptoms, olfactory deficit, mild cognitive impairment, erectile dysfunction, color vision abnormalities, constipation, REM atonia loss, and age represent relevant biomarkers to predict the probability of phenoconversion. Moreover, phosphorylated-α-synuclein (p-α-syn) deposits were detected in skin specimens of iRBD patients and proposed as diagnostic biomarker of underlying synucleinopathy. α-syn deposits were also found in PD retinas.

The aim of this study was to evaluate the PLR and mRGC-mediated contribution to PLR in iRBD.

Methods

This cross-sectional study included 16 iRBD patients consecutively diagnosed according to international diagnostic criteria and 16 healthy controls. We received approval from the local ethical standards committee on human studies (EC Interaziendale Bologna-Imola #16032) and written informed consent was obtained from all patients participating in the study. Exclusion criteria were: spherical/cylindrical refractive errors more than 3 or 2 dioptries; presence of posterior pole pathology including age-related macular degeneration and known optic neuropathies; ocular pressure more than 20 mmHg; severe lens opacity and/or retinal detachment and/or vascular retinal pathology; history of ophthalmologic surgery, except for uncomplicated cataract surgery, performed at least 6 months previously; shift-workers in the last year; and travels through more than one time zone during the last 3 months. Extensive neuro-ophthalmological evaluations were performed by using the protocol previously described.

Controls underwent 7 days actigraphy (MotionWatch 8, CamNtech Ltd., Cambridge, UK) to ascertain absence of sleep disorders. Moreover, we computed the I< O index and none of the controls displayed I< O values below the cut-off of 98.32.

Sleep questionnaires were administered (Epworth Sleepiness Scale [ESS]; Pittsburgh Sleep Quality Index, [PSQI]; Berlin questionnaire; REM sleep Behavior Disorder Screening Questionnaire [RBDSQ]) to evaluate the possible occurrence of sleep disturbances and RBD.

The whole group of iRBD patients was also investigated by means of history-taking looking for non-motor and motor symptoms, neurologic examination including evaluation with the Unified Parkinson’s Disease Rating Scale Part III (UPDRS-III), extensive neuropsychological tests, brain magnetic resonance imaging (MRI), and nigrostriatal dopamine transporter ligand [123I]-ioflupane single-photon emission computed tomography (SPECT) (DaTscan). All iRBD patients underwent nocturnal polysomnography and REM Ation Index (RAI) was computed, using the validated automatic analysis implemented in Hypnolab v. 1.2 software. For all patients we also retrieved data of skin biopsy for p-α-syn deposits by obtaining in total eight 3 mm punches biopsies for each patients (ie, two at the cervical C8 level left and right and two at the distal leg left and right), which were then analyzed according to previously reported methods.

The chromatic pupillometry protocol is described in detail elsewhere. A Ganzfeld ColorDome full-field stimulator (Espion V6, ColorDome Desktop Ganzfeld;
Diagnosys LLC; Lowell, MA, USA) was used. Participants were dark-adapted for 10 minutes, and colored light stimuli were presented to the tested eye and the pupil responses were recorded from the same eye using the Ganzfeld system equipped with an integrated pupillometer. Stimuli consisted of short wavelength (blue flash, mid = 472 nm) and long wavelength (red flash, mid = 632 nm) light flashes of 1 second duration. The integrated pupillometer system measured the pupil diameter at a 100 Hz sampling frequency. The inter-stimulus interval (ISI) was 20 seconds for the rod- and cone- conditions (for both red and blue stimuli), while for the mRGC-condition ISI was 30 seconds for red stimulus and 70 seconds for the blue one. The light conditions used were the following:

- rod-condition: low luminance blue flash (0.001 cd/m², 472 nm) under dark-adaption;
- mRGC-condition: high luminance blue flash (450 cd/m², 472 nm) under dark-adaption;
- cone-condition: red flash (10 cd/m², 632 nm) presented against 6 cd/m² rod-suppressing blue-adapting field.

Data were analyzed using custom MATLAB scripts (MathWorks Inc., Natick, MA, USA) and the calculated pupillometric parameters were transient PLR amplitude, defined as the difference between the normalized baseline and the minimum normalized PLR after stimulus onset (pupil maximum constriction), and post-illumination pupil response (PIPR) for evaluating the mRGC-sustained constriction (PIPR) (Fig. 1C,D).

Baseline normalized pupil size was significantly larger in iRBD patients compared to controls in rod- (P = 0.027) and mRGC- (P = 0.01) conditions (Table 1). Rod-transient PLR amplitude was significantly decreased (P = 0.024) in iRBD patients compared to controls, while mRGC-mediated PIPR did not differ between groups (Table 1). Transient PLR amplitude was not significantly different between iRBD patients and controls under the cone-condition (Table 1).

In iRBD patients there were no significant differences in rod-transient PLR amplitude and PIPR among subgroups with/without autonomic symptoms, hyposmia, and DaTscan abnormalities (data not shown). Furthermore, we found a significant correlation between RAI and rod-transient PLR amplitude (r = 0.55, P = 0.03).

For iRBD patients we evaluated the presence of p-α-syn deposition in skin biopsy (p-α-synpresence: n = 12, 75%; p-α-synabsence: n = 4, 25%; Table S1). A significant difference between iRBD patients with p-α-syn deposition in skin biopsy and controls was evident for the rod-transient PLR amplitude (controls, median [Q1-Q3] = 0.28 [0.22–0.35]; p-α-synpresence, median [Q1-Q3] = 0.19 [0.12–0.27]; \( p_{\text{adjusted}} = 0.043 \) and the baseline normalized pupil size under rod- (controls, median [Q1-Q3] = 5.8 [5.0–6.6]; p-α-synpresence, median [Q1-Q3] = 7.1 [6.6–7.9]; \( p_{\text{adjusted}} = 0.026 \) and mRGC- (controls, median [Q1-Q3] = 5.5 [4.6–5.9], synpresence median [Q1-Q3] = 6.7 [6.2–7.2]; \( p_{\text{adjusted}} = 0.019 \) conditions.

Mean comparisons of OCT measurements for peripapillary Retinal Nerve Fiber Layer (pRNFL) quadrants and macular ganglion cell layer (GCL + sectors) did not show significant differences between iRBD patients and controls (data not shown).

### Results

Table 1 shows the demographics and clinical characteristics of the two groups. Controls and iRBD patients did not significantly differ in terms of age (P = 0.29) and gender distribution (P = 0.15).

Raw pupil traces showed excessive blink artifacts under rod-, mRGC-, and cone-conditions in one, two, and three controls respectively, and in one iRBD patient under the cone-condition and thus were removed from data analysis.

For rod- (Fig. 1A,B) and cone- (Fig. 1E,F) conditions, PLR is characterized by a rapid transient constriction followed by a relatively rapid return to baseline (Fig. 1A, E, B,F). Under mRGC-condition, the PLR is characterized by an initial transient constriction followed by a sustained constriction (PIPR) (Fig. 1C,D).

Discussion

Our exploratory study shows that PLR rod-contribution is impaired in iRBD and correlates with RAI, which is a diagnostic and prognostic marker of iRBD. Interestingly, a significant reduction of PLR amplitude in the rod-condition compared to controls was evident only for iRBD subjects with a documented underlying synucleinopathy, as demonstrated by the findings of positive skin biopsy for p-α-syn deposits in the skin.
TABLE 1  Sociodemographic/clinical characteristics and pupillometric parameters in controls and idiopathic/isolated rapid eye movement (REM) sleep behavior disorder (iRBD) patients

| Parameter                        | Controls       | iRBD patients  | *P* value |
|----------------------------------|----------------|----------------|-----------|
| Number                           | 16 (50%)       | 16 (50%)       |           |
| Gender                           |                |                |           |
| Male                             | 7 (43.8%)      | 12 (75%)       | 0.15      |
| Female                           | 9 (56.2%)      | 4 (25%)        |           |
| Age, years                       | 66.5 (62.25–70.25) | 70.5 (63.5–73.0) | 0.29      |
| Age class, years                 |                |                |           |
| 50–59                            | 2 (12.5%)      | 2 (12.5%)      | 0.63      |
| 60–69                            | 9 (56.2%)      | 6 (37.5%)      |           |
| 70–79                            | 5 (31.2%)      | 8 (50%)        |           |
| Disease duration                 | NA             | 9.2 ± 6.8      | NA        |
| Autonomic dysfunction            | NA             | NA             |           |
| Constipation                     | 4/16 (26.7%)   |               |           |
| Urinary symptoms                 | 4/16 (26.7%)   |               |           |
| Orthostatic hypotension          | 2/16 (12.5%)   |               |           |
| Hyposmia                         | NA             | 8/16 (53.3%)   | NA        |
| Dopamine imaging<sup>a</sup>     | NA             | 4/16 (26.7%)   | NA        |
| Cognitive evaluation             | Normal         | Normal         |           |
| ROD                              |                |                |           |
| Number                           | 15             | 16             |           |
| Baseline normalized pupil size   | (0.001 cd/m<sup>2</sup>, 472 nm) | (0.001 cd/m<sup>2</sup>, 472 nm) |           |
| Median (Q1–Q3)                   | 5.74 (5.03–6.56) | 7.14 (5.64–7.80) | 0.027     |
| Transient peak amplitude         | (0.001 cd/m<sup>2</sup>, 472 nm) | (0.001 cd/m<sup>2</sup>, 472 nm) |           |
| Median (Q1–Q3)                   | 0.29 (0.22–0.35) | 0.23 (0.12–0.27) | 0.024     |
| MELANOPSIN                       |                |                |           |
| Number                           | 14             | 16             |           |
| Baseline normalized pupil size   | (450 cd/m<sup>2</sup>, 472 nm) | (450 cd/m<sup>2</sup>, 472 nm) |           |
| Median (Q1–Q3)                   | 5.47 (4.64–5.95) | 6.81 (5.94–7.19) | 0.01      |
| PIPR (450 cd/m<sup>2</sup>, 472 nm) |              |                |           |
| Median (Q1–Q3)                   | 0.48 (0.45–0.52) | 0.50 (0.45–0.53) | 0.79      |
| CONE                             |                |                |           |
| Number                           | 13             | 15             |           |
| Baseline normalized pupil size   | (10 cd/m<sup>2</sup>, 632 nm) | (10 cd/m<sup>2</sup>, 632 nm) |           |
| Median (Q1–Q3)                   | 3.19 (2.98–3.87) | 3.76 (3.45–4.07) | 0.17      |
| Transient peak amplitude         | (10 cd/m<sup>2</sup>, 632 nm) | (10 cd/m<sup>2</sup>, 632 nm) |           |
| Median (Q1–Q3)                   | 0.24 (0.20–0.28) | 0.20 (0.15–0.27) | 0.22      |

Values are given as number (absolute frequency) or median (Q1–Q3, interquartile range); Chi-square test was performed with categorical variables and Wilcoxon signed-rank test was used with continuous variables.

<sup>a</sup>Reduced nigrostriatal dopaminergic binding assessed by [123I]-ioflupane single-photon emission computed tomography (SPECT) (DaTscan).

Abbreviations: NA, not applicable; iRBD, idiopathic/isolated rapid eye movement (REM) sleep behavior disorder; PIPR, post-illumination pupil response.
The higher baseline pupil diameter and reduced rod-transient amplitude in iRBD unravels a likely parasympathetic dysfunction. This observation is in line with the cholinergic deficiency already reported by previous pupillometry studies in PD.\textsuperscript{14} Moreover, the presence of rod-mediated transient PLR amplitude abnormalities may putatively reflect a pathology affecting mRGC dendrites before hitting the mRGC cell body,\textsuperscript{3} as supported by the absence of PIPR reduction in our cohort of iRBD subjects. The

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Single and mean normalized pupillary light reflex (PLR) curves for the rod-, melanopsin retinal ganglion cell (mRGC)-, and cone- conditions in controls and idiopathic/isolated rapid eye movement (REM) sleep behavior disorder (iRBD) patients. Pupillometric traces obtained under the rod- (A and B), mRGC- (C and D), and cone- (E and F) conditions of the chromatic pupillometric protocol. Light blue (A, B, C, D panels) and red (E, F panels) traces represent single individuals, while black traces (A–F panels) represent the mean waveforms for each group (A, C, E for the control group; B, D, F for the iRBD group). The vertical dotted lines indicate the time range (5–7 seconds from stimulus offset) over which the mRGC-mediated (sustained) amplitude (post-illumination pupil response [PIPR], 450 cd/m\textsuperscript{2}) was measured. [Color figure can be viewed at wileyonlinelibrary.com]}
\end{figure}
significantly reduced transient peak amplitude in conditions exploring the rod-contribution may, in fact suggest an altered contact between rods and mRGCs. mRGCs receive synaptic input from rods and cones through bipolar cells and a direct contact of rod bipolar cells via ribbon synapses in the ON layer of the inner plexiform layer (IPL) with mRGC dendrites has been demonstrated in human retinas. It is plausible to hypothesize that the rod response depends more on the distal dendrites of mRGCs, and consequently that the subsequent reduced dendritic arborization might interfere with the rod input out of proportion to the cones. The occurrence of mRGC dendopathy has been already reported in PD, as well as a specific affection of the rod pathway through the dopaminergic amacrine cells (AII) synaptically contacting mRGCs.

The association of PLR abnormalities with two of the most powerful markers of impending neurodegeneration in iRBD strengthens our results. Indeed, skin biopsy has consistently demonstrated great sensitivity and specificity as an in vivo diagnostic biomarker of an underlying synucleinopathy in iRBD. Similarly, REM sleep without atonia has been identified as one of earliest signs of neurodegeneration and a valuable prognostic biomarker of disease progression, as it increases over time and greater severity is associated with accelerated phenoconversion.

One study limitation is the small sample size. However, relying on our current results, chromatic pupillometry abnormalities might be proposed as a further potential early marker of parasympathetic affection and/or of mRGC dysfunction in iRBD. Longitudinal studies using larger cohorts are needed to validate pupillometry metrics as an adjunctive biomarker and also for the risk stratification of phenoconversion in iRBD.

Acknowledgments: This work was supported by GR-2013-02358026 Italian Ministry of Health grant to C.L.M. We thank the patients and their families. We thank Prof. Gaetano Cantalupo for support in developing and setting the chromatic pupillometry protocol. We also thank Eng. Luca Berti for assistance with pupil traces analysis, Corrado Zenesini for statistical analysis support, and Prof. Jens Hannibal and Prof. Alfredo A. Sadun for their advice.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

References
1. Aranda ML, Schmidt TM. Diversity of intrinsically photosensitive retinal ganglion cells: circuits and functions. Cell Mol Life Sci 2020; 78(3):889–907.
2. Hannibal J, Christiansen AT, Heegaard S, Fahrenkrug J, Kilgaard JF. Melanopsin expressing human retinal ganglion cells: subtypes, distribution, and intraretinal connectivity. J Comp Neurol 2017;525(8):1934–1961.
3. Romagnoli M, Stanzani Maserati M, De Matteis M, et al. Chromatic pupillometry findings in Alzheimer’s disease. Front Neurol 2020;14:780.
4. Joyce DS, Feigl B, Kerr G, Roeder L, Zele AJ. Melanopsin-mediated pupil function is impaired in Parkinson’s disease. Sci Rep 2018;8(1):7796.
5. Ortuno-Lizaran I, Esquiva G, Beach TG, et al. Degeneration of human photosensitive retinal ganglion cells may explain sleep and circadian rhythms disorders in Parkinson’s disease. Acta Neuropathol Commun 2018;6(1):90.
6. Perkins JE, Janzen A, Bernhard FP, et al. Saccade, pupil, and blink responses in rapid eye movement sleep behavior disorder. Mov Disord 2021;36(7):1720–1726.
7. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142(3):744–759.
8. Antelmi E, Pizza F, Donadio V, et al. Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients. Ann Clin Transl Neurol 2019;6(9):1872–1876.
9. Veyts L, Vandenabeele M, Ortuno-Lizaran I, et al. Retinal alpha-synuclein deposits in Parkinson’s disease patients and animal models. Acta Neuropathol 2019;137(3):379–395.
10. Medicine AAoS. International Classification of Sleep Disorders. Diagnostic and Coding Manual. 3rd ed. American Academy of Sleep Medicine: Westchester, IL; 2014.
11. Filardi M, Stefani A, Holzknecht E, Pizza F, Plazzi G, Hogl B. Objective rest-activity cycle analysis by actigraphy identifies isolated rapid eye movement sleep behavior disorder. Eur J Neurol 2020; 27(10):1848–1855.
12. Ferri R, Manconi M, Plazzi G, et al. A quantitative statistical analysis of the submental muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. J Sleep Res 2008;17(1):89–100.
13. Antelmi E, Donadio V, Incensi A, Plazzi G, Liguori R. Skin nerve phosphorylated alpha-synuclein deposits in idiopathic REM sleep behavior disorder. Neurology 2017;88(22):2128–2131.
14. Fotiou DF, Stergiou V, Tsipitsios D, Lathari C, Nakou M, Karlovastis A. Cholinergic deficiency in Alzheimer’s and Parkinson’s disease: evaluation with pupillometry. Int J Psychophysiol 2009;73(2):143–149.
15. Ortuno-Lizaran I, Sanchez-Saez X, Lax P, et al. Dopaminergic retinal cell loss and visual dysfunction in Parkinson’s disease. Ann Neurol 2020;88(5):893–906.
16. Doppler K, Jentschke HM, Schulmeyer L, et al. Dermal phosphorylated alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson’s disease. Acta Neuropathol 2017;133(4): 535–545.
17. Ferri R, Arico D, Cosentino FI, Lanuzza B, Chiari G, Manconi M. REM sleep without atonia versus REM sleep-related motor events: broadening the spectrum of REM sleep behavior disorder. Sleep 2018;41(12).
18. Hogl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. Nat Rev Neurol 2018; 14(1):40–55.
19. Nepozitek J, Dostalova S, Dusek P, et al. Simultaneous tonic and phasic REM sleep without atonia best predicts early phenoconversion to neurodegenerative disease in idiopathic REM sleep behavior disorder. Sleep 2019;42(9).
20. McCarter SJ, Sandness DJ, McCarter AR, et al. REM sleep muscle activity in idiopathic REM sleep behavior disorder predicts phenoconversion. Neurology 2019;93(12):e1171–e1179.

Supporting Data
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.