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CLINICAL REVIEW

Brain imaging findings in idiopathic REM sleep behavior disorder (RBD) – A systematic review on potential biomarkers for neurodegeneration

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SUMMARY

Idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by the loss of physiological atonia of skeletal muscles with abnormal behavior during dream sleep. RBD may be the initial manifestation of neurodegenerative diseases, particularly of α-synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). However, gauging the individual risk of subsequent phenoconversion and making assumptions on the type of disease that may subsequently follow RBD is challenging. Over the past years, a growing number of studies have sought to establish reliable neuroimaging markers to detect neurodegenerative brain changes in RBD subjects at the earliest possible stage.

The present review summarizes recent advances in brain imaging in RBD and provides recommendations for the application of currently available structural and functional neuroimaging modalities to monitor disease progression and risk of subsequent phenoconversion.

Further imaging research applying multimodal approaches is encouraged to enhance accuracy of prognoses. Additionally, more longitudinal studies are warranted to validate findings from cross-sectional studies on RBD progression and risk of subsequent phenoconversion. Aside from enabling reliable prognoses on a single-subject-level in the near future, this might give further insight into RBD pathophysiology, and finally augment the development of intervention strategies and disease-modifying therapies.

Introduction

Idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of physiological atonia of skeletal muscles during dreaming. This results in abnormal nocturnal behavior, such as flailing, punching, kicking and vocalization, self-inflicted injuries or injuries of bed partners [1–3]. According to the International classification of sleep disorders (ICSD-3, 2014) the diagnosis of RBD requires the absence of atonia on electromyography (EMG) during REM sleep with excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or upper or lower limb EMG twitching during polysomnography. Moreover, the exclusion of electroencephalographic epileptiform activity during REM sleep is a prerequisite for the diagnosis [4].

Over the past years, it has increasingly been recognized that RBD is associated with neurodegenerative diseases, particularly with the α-synucleinopathies Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB; [1,2,5–7]). Assumed to be an initial symptom of progressive neurodegeneration, RBD can precede the clinical manifestation of these diseases by many years with risk estimates of up to 33% at 5 y, 76% at 10 y and 91% at 14 y after RBD diagnosis [8,9]. However, individual prognoses concerning the risk of subsequent phenoconversion and likelihood to develop a specific α-

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Abbreviations

CBF	cerebral blood flow
DAT	dopamine transporter
DLB	dementia with Lewy bodies
DTI	diffusion tensor imaging
EMG	electromyography
FC	functional connectivity
HC	healthy controls
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSA	multiple system atrophy
PD	Parkinson's disease
PDRP	Parkinson's disease motor-related pattern
PET	positron emission tomography
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RBD	REM sleep behavior disorder
RBDRP	REM sleep behavior disorder related pattern
REM	rapid eye movement
rs-fMRI	resting-state functional magnetic resonance imaging
SN	substantia nigra
SPECT	single photon emission computerized tomography
TCS	transcranial sonography
VBM	voxel-based morphometry

synucleinopathy are challenging. Therefore, an increasing number of studies are seeking to establish neuroimaging markers to detect neurodegenerative brain changes at the earliest possible stage. We summarize recent advances in brain imaging in RBD and provide recommendations for the application of currently available neuroimaging modalities to monitor disease progression.

Methods

We ran electronic searches for English peer-reviewed journal articles indexed in the PubMed database until February 2016. The following keywords were used for search: “REM sleep behavior disorder OR RBD” AND “imaging; neuroimaging; transcranial sonography; TCS; PET; SPECT; MRI OR MRS”. To identify additional studies that were not retrieved in this initial search, we browsed through reference lists and published reviews focusing on this or similar topics. Only studies on idiopathic RBD without comorbid mental and/or neurologic diseases (e.g., major depression, narcolepsy or neurodegenerative diseases) were included, unless these studies compared RBD patients with additional comorbidities to idiopathic RBD patients. We excluded studies without polysomnographic confirmation of RBD, ictal and single-subject case studies ($n < 5$ RBD patients). We followed PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines to conduct this systematic review [10]. To evaluate the utility of available imaging modalities to monitor RBD progression and estimate the individual risk of subsequent phenoconversion to a progressive neurodegenerative disease, we performed quality assessments of currently available data. Based on the classification suggested by Wintermark et al. [11] we assigned corresponding classes of recommendation for each imaging technique (Table 1).

Table 1
Classes of recommendation.[a]

Class I	Conditions for which there is evidence for and/or general agreement that the imaging technique is useful
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness
Class II-a	Weight of evidence/opinion is in favor of usefulness
Class II-b	Usefulness is less well-established
Class III	Conditions for which there is evidence and/or general agreement that a procedure is not useful and in some cases may be harmful

[a] From Wintermark et al. [11].

Radiotracer imaging

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) in combination with a variety of radiotracers can be used to explore striatal dopaminergic integrity, brain metabolism and brain perfusion (for a detailed review see [12]). Table 2 provides an overview of the studies on radiotracer imaging in RBD that met our inclusion criteria. The major findings are summarized below.

Presynaptic dopaminergic imaging

Various tracers can be applied with PET and SPECT to investigate presynaptic dopaminergic function. The most commonly used SPECT radiotracer is [^{123}I]FP-CIT (*N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane). It measures the presynaptic dopamine transporter (DAT) density and therefore is also referred to as DAT-scan [12]. PET imaging is usually combined with [^{18}F]FDOPA (L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine) or [^{18}F]FMT (6-[^{18}F]fluoro-l-*m*-tyrosine) to assess activity of the aromatic L-amino acid decarboxylase, converting L-DOPA to dopamine [12,13]. Alternatively, ^{11}C-labeled ligands such as DTBZ (2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11bH-bezo[α]-quinolizine) can be utilized to measure type-2 vesicular monoamine transporter availability which facilitates collection of dopamine from the cytoplasm and storage for synaptic release [12].

Presynaptic PET and SPECT have been shown to be able to identify PD and related disorders in very early disease stages [12,14]. They have therefore been in the focus of several studies on RBD, with reductions of presynaptic striatal dopamine levels being a consistent finding. Of note, dopamine depletion has been found to be most pronounced in the putamen [15–24], an intriguing finding, given that loss of dopaminergic integrity in PD typically begins in the dorsal putamen [25]. Correspondingly, striatal dopaminergic integrity was found to be associated with motor function in RBD [15]. Moreover, progressive decrease of striatal DAT-uptake has been shown from healthy controls (HC) to “subclinical RBD” (REM sleep without atonia on polysomnography, but absence of abnormal nocturnal behaviors) to manifest RBD to PD [19,26]. Similarly, continuous loss of presynaptic dopaminergic function has been observed in a 3-y longitudinal RBD study [20]. Interestingly, the three subjects displaying the lowest tracer uptake values at baseline were subsequently diagnosed with PD [20].

Taken together, the available data indicate that imaging of presynaptic dopaminergic integrity is suitable to monitor disease progression and identify individuals at specific risk to

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Table 2
Radiotracer imaging in RBD.

	Study sample	Tracer	Tracer uptake		Tracer uptake	
	n (n♂; age in y±SD; RBD disease duration in y±SD)		RBD *versus* HC		RBD *versus* PD	
Presynaptic imaging						
Albin et al. (22)	RBD 6 (5♂; 68±n.a.; n.a.) HC 19 (11♂; 66)	[^{11}C]DTBZ	putamen, nucleus caudatus: striatum:	↓ ↔	n.a.	
Arnaldi et al. (26)	RBD 12 (12♂; 66.4±7.5; 4.3±3.7) PD-RBD 16 (8♂; 67.2±7.2) PD+RBD 24 (16♂; 69.4±6; 3.7±5.3)	[^{123}I]FP-CIT	n.a.		*specific binding ratios:* RBD *versus* PD-RBD putamen: putamen to caudate: RBD *versus* PD+RBD caudate: putamen: putamen to caudate:	 ↔ ↑ ↔ ↑ ↑
Arnaldi et al. (24)	RBD 20 (19♂; 66±7.1; n.a.) HC 23 (10♂; 70±7.7)	[^{123}I]FP-CIT	putamen, nucleus caudatus: midbrain, pons: thalamus:	↓|↓ ↔ ↔|↔	n.a.	
Eisensehr et al. (16)	RBD 5 (4♂; 68.5±7.5; n.a.) HC 7 (5♂; 63.0±6.4) PD 14 (10♂; 50.3±9.9)	[^{123}I]IPT	putamen, nucleus caudatus, striatum:	↓|↓	putamen, striatum: nucleus caudatus:	↑|↑ ↔|↔
Eisensehr et al. (19)	sRBD 8 (6♂; 62.3±13.5; n.a.) RBD 8 (7♂; 69.2±7.6; n.a.) HC 11 (9♂; 61.6±8.2) PD 8 (5♂; 57.2±6.6)	[^{123}I]IPT	sRBD *versus* HC putamen, nucleus caudatus, striatum: sRBD *versus* RBD putamen: nucleus caudatus, striatum:	 ↓|↓ ↔|↔ ↔|↓	sRBD *versus* PD putamen, nucleus caudatus, striatum:	 ↑|↑
Iranzo et al. (18)	RBD 43 (37♂; 70.2±6.9; 9.5±5.1) HC 18 (12♂; 70.1±7.1)	[^{123}I]FP-CIT	putamen: nucleus caudatus:	↓|↓ ↔|↓	n.a.	
Iranzo et al. (20)	RBD 20 (18♂; 70.6±6.0; 9.6±6.0) HC 20 (15♂; 69.5±6.8)	[^{123}I]FP-CIT	baseline and after 3 years putamen, nucleus caudatus:	 ↓|↓	n.a.	
Kim et al. (21)	RBD 14 (11♂; n.a.) HC 12 (8♂; 63.3±5.7) PD 14 (11♂; 67.0±4.1)	[^{123}I]FP-CIT	putamen: nucleus caudatus,striatum:	↓ ↔	putamen: nucleus caudatus,striatum:	↓ ↔
Miyamoto et al. (23)	RBD normTCS 10 (10♂; 66.0±5.8; 3.9±1.7) RBD pathTCS 9 (9♂; 66.8±3.9; 4.3±2.1)	[^{18}F]FMT	RBD pathTCS *versus* normTCS putamen, nucleus caudatus: ↓			
Rupprecht et al. (15)	RBD 28 (20♂; 66.3±8.0; 6.7±6.3)	[^{123}I]FP-CIT	↓ in 4 RBD, most pronounced in putamen in 3			
Stiasny-Kolster et al. (17)	sRBD 2 (0♂; 46.6±12.6; n.a.) RBD 11 (6♂; 46.3±14.2; 20.0±25.5) HC 10 (n.a.♂; 61.1±17.5)	[^{123}I]FP-CIT	↓ in 2 out of 3 RBD without concomitant diseases			
Unger et al. (62)	RBD 7 (out of 12: 11♂; 59±10.5; n.a.)	[^{123}I]FP-CIT	reduced and/or asymmetric uptake in 4			
Postsynaptic imaging						
Eisensehr et al. (16)	RBD 5 (4♂; 68.5±7.5; n.a.) HC 7 (6♂; 66.1±2.0) PD 14 (10♂; 50.3±9.9)	[^{123}I]IBZM	striatum:	↔|↔	n.a.	
Eisensehr et al. (19)	sRBD 8 (6♂; 62.3±13.5; n.a.) RBD 8 (7♂; 69.2±7.6; n.a.) HC 10 (8♂; n.a.)	[^{123}I]IBZM	sRBD *versus* HC and RBD striatum:	 ↔|↔	n.a.	
Perfusion SPECT						
Dang-Vu et al. (45)	RBD(-) 10 (8♂; 65.5±7.2; 17.7±11.6) RBD(+) 10 (8♂; 70.3±6.6; 10.5±5.8) HC 10 (n.a.)	[^{99m}Tc]ECD	RBD(+) *versus* HC hippocampus: pons: RBD(-) *vs* HC	 ↑|↑ ↑ ↔|↔	RBD(+) *versus* RBD(-) hippocampus:	 ↑|↑
Hanyu et al. (44)	RBD 24 (21♂; 68±7; 6±5) HC 18 (9♂; 70±8)	[^{99m}Tc]ECD	cerebellum, parietal lobe: occipital lobe: limbic lobe:	↓|↓ ↓|↔ ↔|↓	n.a.	
Holtbernd et al. (38)	RBD 17 (14♂; 68.9±4.8; 12.8±9.5) HC 17 (n.a.; 66.6±6.0)	[^{99m}Tc]ECD	PDRP regions: pons, globus pallidus, putamen, cerebellum:	 ↑	RBD(+) *versus* RBD(-) pons:	 ↑
Mazza et al. (42)	RBD 8 (7♂; 69.9±8.2; 7.5±4.8) HC 9 (67.4±6.8)	[^{99m}Tc]ECD	pons, putamen: hippocampus: frontal and temporo-parietal lobe:	↑|↑ ↑|↔ ↓|↓	n.a.	
Sakurai et al. (43)	RBD 9 (7♂; 71.1±3.2; 6.5±5.1) HC 18 (9♂; 70.4±8.1)	[^{123}I]IMP	RBD baseline *versus* subsequent SPECT (after 23±9 months) posterior cingulate: ↔|↓			
Vendette et al. (40)	RBD 20 (13♂; 65.0±7.7; 11.1±8.7) HC 20 (15♂; 67.4±6.4)	[^{99m}Tc]ECD	frontal gyrus: precuneus: putamen, hippocampus: pons, postcentral gyrus, temporal lobe:	↓|↓ ↓ ↑|↑ ↑	n.a.	

(*continued on next page*)

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Table 2 (*continued*)

	Study sample	Tracer	Tracer uptake		Tracer uptake	
	n (n♂; age in y±SD; RBD disease duration in y±SD)		RBD *versus* HC		RBD *versus* PD	
Vendette et al. (41)	RBD+MCI 10 (7♂; 68.5±5.7; 13.4±10.0) RBD-MCI 10 (5♂; 65.64±8.22; 8.0±5.8) HC 20 (15♂; 67.4±6.4)	[^{99m}Tc]ECD	RBD+MCI *vs* HC middle frontal, cuneus: precuneus, inferior parietal lobe: superior occipital and temporal gyrus: parahippocampus: hippocampus: paracentral gyrus: RBD-MCI *vs* HC middle frontal gyrus: superior frontal gyrus: parahippocampus: hippocampus:	↓|↓ ↓|↔ ↔|↓ ↑|↑ ↔|↑ ↑|↔ ↓|↓ ↔|↓ ↑|↑ ↔|↑	RBD+MCI *vs* RBD-MCI cuneus, superior temporal gyrus: hippocampus: putamen: paracentral gyrus:	↓|↓ ↔|↑ ↑|↑ ↑|↔
Metabolic PET						
Ge et al. (39)	RBD 21 (17♂; 65.0±5.6; 5.7±3.5) HC 21 (17♂; 62.5±7.5)	[^{18}F]FDG	superior temporal gyrus: transverse temporal gyrus: occipital cortex, lingual gyrus: precuneus, cerebellar tonsil: superior frontal gyrus, supplementary motor area, cingulate, insula, pons, inferior parietal lobe, (para-)hippo-campus:	↑|↓ ↓|↔ ↓|↓ ↔|↑ ↑|↑	n.a.	
Holtbernd et al. (38)	RBD 10 (10♂; 63.5±9.4; n.a.) HC 10 (n.a.; 62.7±8.6)	[^{18}F]FDG	PDRP regions: pons, globus pallidus, putamen, thalamus:	 ↑	n.a.	
Wu et al. (37)	Cohort A: RBD 21 (17♂; 65.0±5.6; 5.7±3.5) HC 21 (17♂; 62.5±7.5) Cohort B: RBD 15 (12♂; 65.5±6.0; 5.5±4.0) HC 15 (10♂; 60.5±7.6) Cohort C: mild PD 21 (12♂; 62.6±5.0) moderate PD 16 (5♂; 56.9±12.2)	[^{18}F]FDG & [^{11C}]CFT	RBDRP Cohort A RBD *vs* HC: Cohort B RBD *vs* HC: PDRP Cohort A RBD *vs* HC: Cohort B RBD *vs* HC:	 ↑ ↑ ↑ ↑	RBDRP RBD(A) *vs* mild PD: RBD(A) *vs* moderate PD: PDRP RBD(A) *vs* mild PD: RBD(A) *vs* moderate PD:	 ↔ ↑ ↔ ↓

Abbreviations: HC = healthy controls; n.a. = not available; normTCS = normal transcranial sonography; pathTCS = pathological transcranial sonography; PD = Parkinson's disease; PD+RBD = PD with comorbid RBD; PD-RBD = PD without RBD; PET = positron emission tomography; RBD = rapid eye movement sleep behavior disorder; RBD(+) = RBD patients who subsequently developed clinical manifestations of PD or DLB; RBD(-) = RBD patients who did not phenoconvert during follow-up; RBD+MCI = RBD with mild cognitive impairment; RBD-MCI = RBD without mild cognitive impairment; SPECT = single photon emission computed tomography; sRBD = subclinical RBD; ♂ = male; ↔ = unchanged; ↓ = reduced; ↑ = increased; two arrows indicate information for the left|right hemisphere; numbers indicate mean±standard deviation

Brain networks:

PDRP = PD-related pattern: relative increases in sensorimotor, pallidothalamic, pontine, and cerebellar metabolism, associated with decreases in premotor and posterior parietal-occipital metabolism

RBDRP = RBD-related pattern: increased activity in posterior cerebellum, pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri in association with decreased activity in occipital and superior temporal regions

Tracers:

[^{11}C]CFT = 2B-carbomethoxy-3B-(4-fluorophenyl)tropane

[^{11}C]DTBZ = 2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11bH-bezo[α]-quinolizine

[^{18}F]FDG = fluoro-2-deoxy-2-D-glucose

[^{18}F]FMT = 6-[18F]fluoro-l-m-tyrosine

[^{123}I]FP-CIT = *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane (= DAT-Scan)

[^{123}I]IBZM = (S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide

[^{123}I]IMP = N-isopropyl-p-[^{123}I] iodoamphetamine

[^{123}I]IPT = (N)-(3-iodopropen-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane

[^{99m}Tc]ECD = N,N'-1,2-ethylenediylbis-L-cysteine diethyl ester

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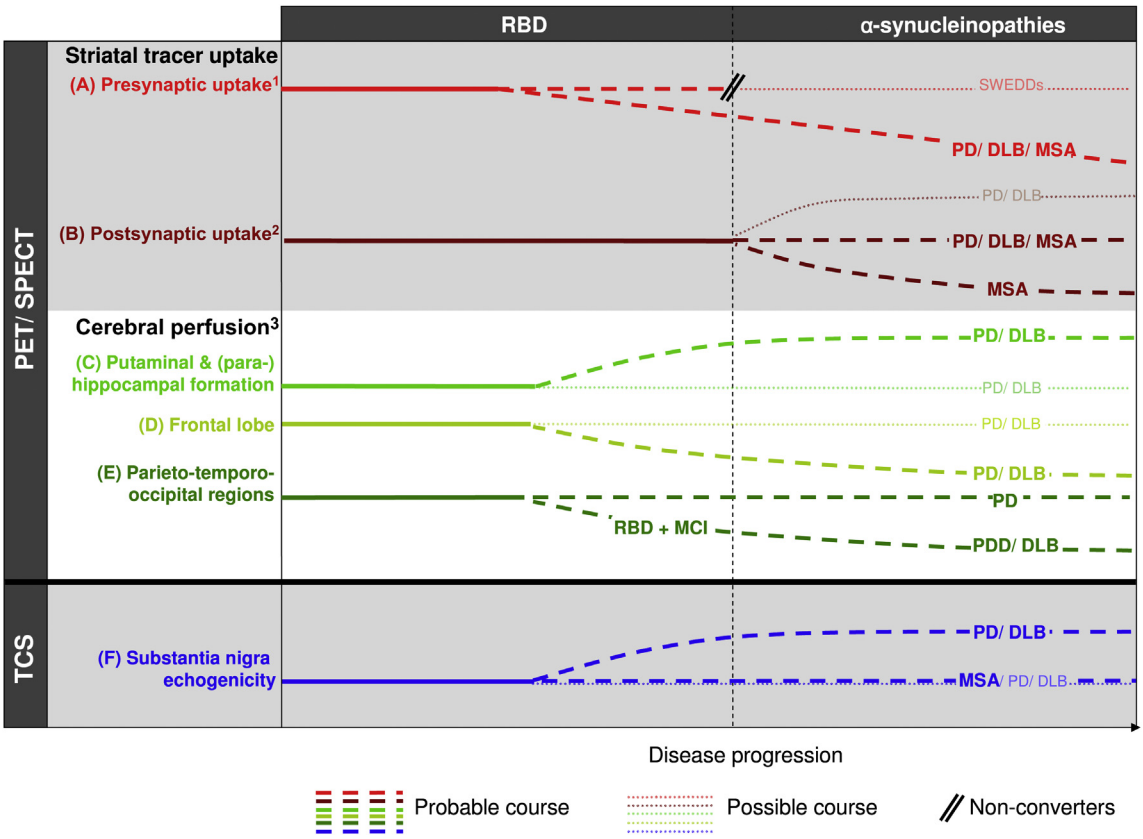

Fig. 1. Schematic illustration of neuroimaging findings as possible indicators for further neurodegeneration. **Legend**: Fig. 1 shows imaging markers for neurodegenerative processes during the stage of RBD, and as it progresses towards the α-synucleinopathies PD, DLB or MSA. **(A)** Presynaptic striatal tracer uptake has been shown to already be reduced in most RBD patients and later on in almost all PD, DLB and MSA patients. RBD patients with normal presynaptic uptake might therefore not phenoconvert (yet) or belong to the group of patients with scans without evidence of dopaminergic deficit (SWEDDs). **(B)** Postsynaptic striatal tracer uptake is usually normal in PD and DLB, although, increased postsynaptic tracer uptake in PD and DLB particularly in early disease stages was also observed. Findings on postsynaptic imaging in MSA are equivocal with tracer uptake either normal or reduced. During the stage of RBD only, postsynaptic tracer uptake has been shown to be normal. **(C)** & **(D)** The majority of PD and DLB patients has been reported to present with increased cerebral perfusion in the putaminal and (para-)hippocampal formation but decreased perfusion in frontal lobe areas. RBD individuals showing this specific pattern of cerebral perfusion might therefore be at increased risk to eventually phenoconvert (to PD or DLB); **(E)** Parieto-temporo-occipital hypoperfusion is a consistent finding in DLB and cognitively impaired PD and has also been observed in RBD patients with MCI. **(F)** SN hyperechogenicity is reported in the majority of PD/DLB patients, however, some PD/DLB as well as MSA patients might present with normal substantia nigra echogenicity. **Abbreviations**: RBD = rapid eye movement sleep behavior disorder; SWEDDS = scans without evidence of dopaminergic deficit (in PD); PD=Parkinson's disease; PDD=Parkinson's disease dementia; DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PET = photon emission tomography; SPECT = single photon emission tomography; TCS = transcranial sonography; [1]most commonly used tracers in presynaptic uptake: [^{123}I]FP-CIT=*N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)nortropane (=DAT-Scan) and [^{11}C]DTBZ = 2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11bH-bezo[α]-quinolizine; [2]most commonly used tracers in postsynaptic uptake: [123I]IBZM=(S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide and various ^{11}C- and ^{18}F-labeled benzamides; [3] most commonly used tracer to measure cerebral perfusion: [99mTc]ECD = N,N′-1,2-ethylenediylbis-L-cysteine diethyl ester.

phenoconvert eventually (Fig. 1). The research field features many studies of a high standard with blind comparisons to other imaging methods [23] and longitudinal assessments of RBD progression [20]. Moreover, many studies included relatively large RBD cohorts ($n \geq 20$; [15,18,20,24]). Despite several methodological differences regarding sample sizes and/or applied imaging techniques and tracers, findings have been very homogenous. Based on this, we assign a class I recommendation for the use of presynaptic dopaminergic imaging in RBD.

Postsynaptic dopaminergic imaging

To assess postsynaptic dopaminergic function PET can be combined with various ^{11}C- and ^{18}F-labeled benzamides, whereas SPECT routinely is performed with [^{123}I]IBZM ((S)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide). Postsynaptic tracer uptake has commonly been reported to be normal in PD and DLB [13,27]. However, particularly in early disease stages, PD patients might present with an increased uptake which has been discussed as a compensatory effect, yet, the underlying mechanisms are not fully understood [13,28]. While several studies have found postsynaptic uptake to be reduced in atypical parkinsonism (e.g., MSA; [13]), there are also contradictory findings showing that normal postsynaptic dopaminergic functioning does not rule out atypical parkinsonism [27,29–31].

This might explain why data on postsynaptic dopaminergic integrity in RBD are scarce. We only identified two studies in this field that met our inclusion criteria and none of these studies found significant differences in postsynaptic dopaminergic integrity between RBD, PD and HC [16,19]. The significance of these data is limited by small sample sizes and a focus on narrow subgroups of patients. So far, postsynaptic dopaminergic imaging is not suggested to monitor RBD progression or to predict the individual risk for subsequent phenoconversion (class II-b recommendation).

Metabolic imaging

^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET reflects cerebral metabolic activity, and is routinely applied to characterize brain

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metabolism in neurodegenerative disorders [13,32]. For PD, a highly specific metabolic brain network has been identified which is associated with the motor symptoms of the disease (PD motor-related pattern [PDRP]; [33]). It is characterized by relative metabolic increases in pallidothalamic, pontine and cerebellar regions and concomitant decreased activity in premotor and parietal regions [33]. PDRP-expression correlates with disease progression and severity, and is not expressed in atypical parkinsonism [34,35]. It also precedes motor symptom onset by several years and might therefore suit as a biomarker in "prodromal" PD [36]. Indeed, PDRP-expression has been found to be elevated in RBD [37,38] comparable to that observed in the "presymptomatic" hemispheres (i.e., hemispheres ipsilateral to the body side with motor symptoms) of early stage PD patients [38]. Moreover, a spatial covariance pattern being specific for RBD has been identified recently [37]. It is characterized by increased activity in the pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, with concurrent relative metabolic decreases in occipital and superior temporal regions, and shows overlap with PDRP-topography. In line with this, altered brain metabolism in various cortical and subcortical areas has been shown to significantly correlate with RBD disease duration, pointing towards progression of the disease [39].

The homogenous results provide substantial evidence that metabolic imaging is suitable to monitor RBD progression. However, there is a need for longitudinal studies confirming the utility of metabolic imaging to predict subsequent phenoconversion in RBD (class II-a recommendation).

Imaging of cerebral perfusion

Most studies investigating alterations of cerebral blood flow (CBF) in RBD utilized [^{99m}Tc]ECD (N,N′-1,2-ethylenediylbis-L-cysteine diethyl ester)-SPECT. Regional CBF reductions have been reported in frontal [40–42], temporo-parietal [40,42,43], parieto-occipital [43,44], limbic and cerebellar [44] regions. In contrast, increased CBF has been observed mainly in parahippocampal, pontine and putaminal regions [40–42,45].

Reduced frontal lobe perfusion has also been described in PD [46,47], while occipito-parieto-temporal hypoperfusion is a consistent finding in DLB and cognitively impaired PD patients [46–48]. RBD patients with hypoperfusion in these regions might therefore be at increased risk for cognitive impairment. This hypothesis is underlined by a recent study comparing RBD patients with and without mild cognitive impairment (MCI). While both groups displayed reduced frontal lobe CBF, RBD patients with MCI showed additional occipito-parieto-temporal hypoperfusion [41]. Along these lines, parieto-occipital hypometabolism has been shown to worsen over time in RBD, suggesting progressive functional decline [43]. Apart from this, increased hippocampal CBF has been shown to be predictive of subsequent development of PD/DLB in a 3-y follow-up study [45].

Additional findings from network-level-analyses suggest that abnormally increased PDRP-expression on ECD-SPECT is indicative of subsequent phenoconversion, and that a logistical regression model based on PDRP-expression and subject age at baseline enables accurate prediction of final phenoconversion status [38].

In summary, the available data suggest that perfusion based SPECT is valuable in the identification of RBD individuals at increased risk to eventually phenoconvert, but further evidence is needed to clarify the underlying mechanisms of the multifaceted findings (class II-a recommendation).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) assesses brain structure and function without exposing subjects to ionizing radiation. It has been applied in several studies on functional and structural brain changes in RBD (Table 3) with novel sequences allowing for the investigation of brain metabolism, microstructure and iron content.

Conventional structural MRI

One of the earliest studies on brain structural alterations in RBD revealed multifocal lesions in dorsal pontomesencephalic and periventricular regions in five out of six patients [49]. However, subsequent studies did not confirm these findings, but reported rather nonspecific brain changes such as single white matter lacunes [19,42], ventricular enlargement [50], universal cortical [42,51] and/or frontal lobe atrophy [51,52] and/or atrophy of posterior cortical regions [51]. The specificity of these findings is limited as brain atrophy and white matter lesions commonly occur in the elderly [53]. Moreover, one study using voxel-based morphometry (VBM) failed to detect significant white matter changes in RBD compared to age-matched HC [54]. However, the same study reported increased grey matter density of both hippocampi and parahippocampal gyri of RBD patients [54]. In contrast, grey matter reduction in the left parahippocampal gyrus of RBD patients has been reported in another VBM-study with a similar sample size (20 RBD patients, 18 HC; [55]). The latter study also reported bilateral atrophy of the anterior lobes of the cerebellum and the tegmental portion of the pons [55]. Yet, other VBM analyses revealed volume loss adjecent to the right superior frontal sulcus [51] and bilateral putamen of RBD patients [56]. Interestingly, putaminal volume was also reduced in RBD compared to early stage PD in the latter study. The authors suggest compensatory effects possibly related to the manifestation of motor deficits in PD to be the reason for this putaminal volume increase in PD compared to RBD [56]. Given that putaminal atrophy typically is observed in MSA [57–60], putaminal volume reduction in RBD might also indicate emerging MSA pathology. However, taking into account the rather low incidence of MSA, it does not seem likely that all of these patients subsequently will develop MSA and none PD.

With the findings from conventional structural MRI being highly inconclusive (class II-b recommendation) this technique has yet to prove its usefulness to monitor RBD progression.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) allows for the assessment of the microstructural integrity of the brain by quantification of diffusion-driven displacement of water molecules. It has been extensively used to study microstructural alterations in PD and atypical parkinsonism, and has shown potential for early disease detection and in differential diagnoses of parkinsonian syndromes [61]. In spite of that, only few studies have employed DTI in RBD and findings are heterogeneous.

Increased mean diffusivity (average magnitude of molecular displacement) and reduced fractional anisotropy (degree of anisotropy of a diffusion process) and axial diffusivity (magnitude of molecular displacement parallel to axonal tracts) have been reported for different brainstem regions [54,62], pointing to the pivotal role of microstructural brainstem damage in RBD pathophysiology [1,63]. Additionally, Unger et al. observed altered substantia nigra (SN) fractional anisotropy. This finding has also been reported by several studies on PD [61] and might indicate

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Table 3
Magnetic resonance imaging and spectroscopy in RBD.

	Study sample n (n♂; age in y±SD; RBD disease duration in y±SD)	HC, RBD, PD overall	RBD *versus* HC or young HC	RBD *versus* PD or early PD
Conventional structural magnetic resonance imaging				
Culebras et al. (49)	RBD 6 (4♂; range: 64 to 74; n.a.)	RBD: -multifocal lesions in periventricular (n=5) & dorsal pontomesencephalic areas (n=3)	n.a.	n.a.
Eisensehr et al. (19)	sRBD 8 (6♂; 62.3±13.5; n.a.) RBD 8 (7♂; 69.2±7.6; n.a.) HC 11 (9♂; 61.6±8.2)	HC: - white matter lesions: 27% RBD: -white matter lesions: 25%	n.a.	n.a.
Ellmore et al. (56)	RBD 5 (4♂; 52.6±10.1; n.a.) early PD 5 (4♂; 60.0±9.6) HC 7 (4♂; 54.0±7.8) young HC 10 (5♂; 26.3±2.8)	RBD: -negative correlation of brain volume with age -positive correlation of quality of life with normalized putamen volumes & of performance on timed gait task with normalized nucleus caudatus & putamen volumes	whole brain volume: ↔ nucleus caudatus volume: ↔|↔ putaminal volume: ↓|↓	whole brain volume: ↔ nucleus caudatus volume: ↔|↔ putaminal volume: ↑|↔
Hanyu et al. (55)	RBD 20 (17♂; 68±7; 6±5) HC 18 (9♂; 71±8)	n.a.	cerebellar volume (anterior lobes): ↓|↓ pontine volume (tegmental portion): ↓ parahippocampal volume: ↓|↔	n.a.
Lee et al. (50)	RBD 15 (10♂; 62.8±7.4; n.a.) HC 20 (12♂; 60±6.4)	n.a.	grey and white matter volumes: ↔ lateral ventricle volumes: ↑	n.a.
Mazza et al. (42)	RBD 8 (7♂; 69.9±8.2; 7.5±4.8) HC 9 (n.a.; 67.4±6.8)	single white matter lacunes and/or mild cortical atrophy: HC: 33% RBD: 50%	n.a.	n.a.
Rahayel et al. (51)	RBD 24 (20♂; 64.2±7; 9.3±9) HC 42 (28♂; 63.3±7.1)	RBD: -no correlation between cortical thickness & UPDRS-III score or RBD duration	corticometry: mean global cortical thickness: ↓ medial frontal lobe, dorsolateral superior frontal gyrus, lingual gyrus, fusiform gyrus: ↔|↓ voxel based morphometry: volume around superior frontal sulcus: ↔|↓	n.a.
Shirakawa et al. (52)	RBD 20 (21♂; 63.4±8.5; n.a.) HC 7 (7♂; 77.4±4.2)	HC: -frontal lobe atrophy: 71% RBD: -frontal lobe atrophy: 45%	n.a.	n.a.
Diffusion tensor imaging				
Rahayel et al. (51)	RBD 24 (20♂; 64.2±7; 9.3±9) HC 42 (28♂; 63.3±7.1)	n.a.	mean diffusivity, axial diffusivity, fractional anisotropy, radial diffusivity: ↔	n.a.
Scherfler et al. (54)	RBD 26 (21♂; 67.4±4.9; 9.2±6.4) HC 14 (10♂; 64.5±5.2)	n.a.	mean diffusivity: Mesencephalic and pontine tegmentum, formation reticularis: ↑ fractional anisotropy: mesencephalic tegmentum: ↓	n.a.
Unger et al. (62)	RBD 12 (11♂; 59±10.5; n.a.) HC 12 (3♂; 56.8±10.6; n.a.)	n.a.	fractional anisotropy: fornix: ↓ white visual stream: ↓ superior temporal lobe: ↓|↔	n.a.
Resting-state functional magnetic resonance imaging				
Ellmore et al. (68)	RBD 10 (6♂; 57±2.7; n.a.) HC 10 (4♂; 57±2.4) PD 11 (7♂; 62±2.5)	n.a.	cluster correlations: putamen-SN: ↓|↔ cuneus, precuneus, Brodmann area 7-SN: ↔|↑ superior occipital gyrus: ↔|↑	cluster correlations: putamen-SN: ↑|↔ cuneus, precuneus, Brodmann area 7-SN: ↔|↑ superior occipital gyrus: ↔|↓
Magnetic resonance imaging of iron deposition				
Lee et al. (50)	RBD 15 (10♂; 62.8±7.4; n.a.) HC 20 (12♂; 60±6.4)	n.a.	transverse relaxation rate (R2*): ↔|↔	n.a.
Magnetic resonance spectroscopy				
Iranzo et al. (76)	RBD 15 (15♂; 65.7±6.4; 5.2±3) HC 15 (15♂; 64.3±7.1)	n.a.	N-acetylaspartate, creatine, choline, creatine & myoinosito, creatine ratios: mesencephalon, pons: ↔	n.a.

Abbreviations: HC = healthy controls; n.a. = not available; PD = Parkinson's disease; RBD = rapid eye movement sleep behavior disorder; SN = substantia nigra; sRBD = subclinical RBD; UPDRS-III = unified Parkinson's disease rating scale; ♂ = male; ; ↔ = unchanged; ↓ = reduced; ↑ = increased; two arrows indicate information for the left|right hemisphere; numbers indicate mean±standard deviation

immanent neurodegenerative processes. However, absence of correlations between RBD disease duration and DTI measures [54] questions the suitability of this technique to monitor disease progression. That said, another study did not detect differences between RBD and HC in any DTI values [51]. Longitudinal assessment would be warranted to clarify these contradictory findings.

Taken together, DTI provides some evidence for a pathophysiological overlap between RBD and PD. However, findings are equivocal and the utility of DTI to monitor RBD progression has to be further evaluated (class II-b recommendation).

Resting state functional MRI

Brain activity at rest can be investigated by resting-state functional MRI (rs-fMRI) assessing spontaneous fluctuations in the blood-oxygen-level dependent signal [64]. Various studies identified widespread but disease-specific functional connectivity (FC) alterations in PD [65], DLB [66] and MSA [67].

To the best of our knowledge, only one study employed rs-fMRI in RBD, reporting reduced FC between the left putamen and the SN. Of note, FC between these regions was still higher in RBD as compared to PD, indicating a continuous spectrum of decline in FC [68]. However, no longitudinal data are available, and thus no firm conclusions can be drawn with respect to RBD progression.

The current availability of no more than one study only allows for assignment of a class II-b recommendation for rs-fMRI in RBD. However, with the encouraging findings from rs-fMRI in parkinsonian syndromes [65–67], this method is promising in its future application to RBD patients.

MRI of iron deposition

Increased brain iron deposition has been proposed to contribute to the formation of free radicals leading to oxidative damage and cell death, and consequently has been associated with human brain neurodegenerative processes [69]. While increased nigral iron content has been reported in PD, data on iron deposition in MSA and DLB are not sufficient to draw general conclusions [70]. As for RBD, the only existing study failed to demonstrate iron deposition alterations when comparing 15 patients to 20 HC [50]. These results might originate from insufficient power of the data and/or too small effects to adjust for possible confounding variables. Alternatively, they might mirror an RBD cohort not yet phenoconverting. More and longitudinal studies are required to further explore a possible association of brain iron deposition and RBD progression. To date, the limited data in RBD only allow for a class II-b recommendation for this modality.

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) enables *in vivo* investigations to determine the presence and concentration of various tissue metabolites [71]. In humans, proton MRS (^{1}H-MRS) can be applied to monitor brain metabolism [72]. It has been employed in several studies on MSA [73], PD [74] and dementia [75] giving valuable insights into disease pathogenesis.

However, we could only indentify one study on brain metabolism in RBD that met our inclusion criteria which did not find any alterations in metabolic ratios in the midbrain or brainstem in RBD compared to HC [76].

Thus, no firm conclusions can be drawn regarding the utility of MRS to assess RBD pathology and/or progression (class II-b recommendation).

Transcranial sonography

Transcranial sonography (TCS) visualizes echogenicity of brain tissue. SN hyperechogenicity is reported in the majority of PD

Table 4
Transcranial sonography in RBD.

	Study sample	SN hyperecheogenicity			
	n (n♂; age in y±SD; RBD disease duration in y±SD)	HC	RBD		PD
Iranzo et al. (18)	RBD 39 (out of 43: 37♂; 70.2±6.9; 9.5±5.1)	11%	36.0%		n.a.
	HC 149 (132♂; 68.7±7.7)		*Phenoconversion at 2.5-y follow-up:*		
			-RBD SN-:	*12.0%*	
			-RBD SN+:	*35.7%*	
Iranzo et al. (83)	RBD 51 (out of 55: 47♂; 68.9±7.8; 8.9±5.3)	n.a.	34.5%		n.a.
			Phenoconversion at 5-y follow-up:		
			-RBD SN-:	*34.4%*	
			-RBD SN+:	*42.0%*	
Iwanami et al. (80)	RBD 34 (34♂; 67.9±6.1; 5.3±6.7)	9.5%	41.2%		52.6%
	PD 17 (17♂; 66.4±6.7)		*-RBD SN+ & hyposmia:*	*26.5%*	
	HC 21 (21♂; 64.4±5.8)		*-RBD SN+ & anosmia:*	*11.8%*	
Miyamoto et al. (23)	RBD 19 (19♂; 66.4±4.9; 3.5±1.8)	n.a.	47.4%		n.a.
			-RBD SN+ versus RBD SN-: reduced putaminal & caudate [^{18}F]FMT uptake		
Rupprecht et al. (15)	RBD 28 (20♂; 66.3±8.0; 6.7±6.3)	n.a.	53.6%		n.a.
			-RBD SN- & mild motor signs:	*30.7%*	
			-RBD SN+ & mild motor signs:	*86.7%*	
Shin et al. (84)	RBD 12 (out of 15: 8♂; 65.2±8.7; 5.6)	16.0%	50.0%		87.5%
	PD 24 (out of 30: 21♂; 62.3±6.3)		*-SN+ & olfactory abnormality*	*50.0%*	
	HC 25 (out of 30: 17♂; 61.6±5.1)				
Stockner et al. (79)	RBD 51 (out of 55: 47♂; 68.9±7.8; 8.9±5.3)	10.7%	37.3%		n.a.
	HC 149 (out of 165: 141♂; 69.0±7.7)				
Unger et al. (81)	RBD 5 (5♂; 66±2.3; 4±2.6)	n.a.	40.0%		n.a.
Vilas et al. (82)	RBD-D 34 (out of 40:34♂; 71.8±6.2; 10.4±6.8)	28.8%	62.7%		n.a.
	RBD+D 25 (out of 32:19♂; 70.9±7.3; 10.0±7.6)		*-RBD+D*	*72.0%*	
	HC 59* (out of 71:49♂; 70.7±6.1)		*-RBD-D*	*55.9%*	

Abbreviations: [^{18}F]FMT = 6-[^{18}F]fluoro-l-m-tyrosine; HC = healthy controls; n.a. = not available; PD = Parkinson's disease; RBD = rapid eye movement sleep behavior disorder; RBD+D = RBD with comorbid depression; RBD-D = RBD without depression; RBD SN+ = RBD with baseline substantia nigra hyperechogenicity; RBD SN- = RBD with normal baseline substantia nigra echogenicity; ♂ = male; *18.3% suffered from depression; numbers indicate mean ± standard deviation

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patients [77] and the risk for subsequent PD has been shown to be significantly increased in individuals with hyperechogenic compared to normechogenic SN in a 3-y multicenter follow-up study of 1847 elderly [78]. Moreover, TCS has been proposed to be useful in the differential diagnosis of parkinsonian syndromes [77].

Several studies have applied TCS in RBD (Table 4). Stockner and colleagues observed SN hyperechogenicity in a cohort comprised of 51 RBD patients compared to 149 HC. However, at the individual level, only 37% of RBD patients showed pathologic SN echogenicity [79]. Similarly, other studies reported SN hyperechogenicity in about 40%–55% of RBD patients [23,80–82] and in about 70% of RBD patients with comorbid depression [82]. Of note, SN hyperechogenicity has also been detected in approximately 10% of HC [79,80].

Longitudinal follow-up showed that within 2.5 y 36% of RBD individuals [18] and within 5 y 42% of RBD individuals [83] with SN hyperechogenicity at baseline phenoconverted, demonstrating the predictive value of TCS. However, 12% with normal SN echogenicity at baseline also developed a neurodegenerative disorder within 2.5 y [18], and 34% within 5 y [83].

Some authors have suggested that combining TCS with other imaging modalities might increase accuracy of prognosis. For example, combination of TCS with FP-CIT-SPECT revealed 100% sensitivity and 55% specificity to predict subsequent phenoconversion within the following 2.5 y [18]. Additional assessments of behavioral features commonly observed in RBD, e.g., hyposmia and mild motor impairment, may also enhance the predictive value of TCS [15,80,84].

Taken together, SN hyperechogenicity might act as a vulnerability marker for further neurodegeneration. However, due to the rather low prognostic sensitivity and specificity when used alone, we only propose a class II-a recommendation for the use of TCS in RBD.

Practice points

1) RBD is known to be an initial symptom of progressive neurodegeneration, but individual prognoses concerning the risk of subsequent phenoconversion and likelihood to develop a distinct α-synucleinopathy are challenging.
2) Neuroimaging modalities might help in identifying neurodegenerative brain changes in RBD at the earliest possible stage and in giving prognoses on the course of the disease.
3) Presynaptic radiotracer imaging is suitable to monitor disease progression and to identify individuals at specific risk to phenoconvert, but does not allow assumptions on the entity of subsequent neurodegenerative disorder.
4) TCS is useful to identify RBD subjects at risk to subsequently phenoconvert, but is not sensitive in all cases and should be combined with other imaging modalities and/or behavioral assessments.
5) There is substantial evidence that metabolic imaging and imaging of cerebral perfusion is suitable to monitor RBD progression. However, there is a need for further studies confirming the utility of these methods to predict subsequent phenoconversion.
6) Imaging of cerebral perfusion might identify RBD subjects at risk for future cognitive decline.
7) Postsynaptic radiotracer imaging, MRI and MRS are not suitable as a biomarker for further neurodegeneration in RBD, yet.

Conclusions

Over the past years neuroimaging has enhanced our understanding of RBD pathophysiology and its association with α-synucleinopathies. Although there is no gold standard, an increasing number of studies have provided encouraging results suggesting that various imaging modalities can augment the assessment of RBD progression and allow for the identification of individuals at risk for subsequent phenoconversion to progressive neurodegenerative disease.

Imaging of presynaptic dopaminergic function has shown that striatal dopamine levels are reduced in RBD. A decline over time and dopaminergic depletion are predictive of subsequent phenoconversion. Moreover, RBD patients exhibit consistent network level metabolic abnormalities strikingly similar to those observed in PD patients indicating pathophysiological commonalities between these diseases. Findings from perfusion SPECT show that CBF in posterior cortical and (para)hippocampal areas is abnormal in many RBD subjects and may be associated with future cognitive decline. Furthermore, the expression of PD-like network level abnormalities seems to be indicative of subsequent phenoconversion to PD, DLB or MSA.

Reports from conventional structural MRI, rs-fMRI, DTI and MRS are less coherent, whereas TCS might be useful to identify RBD subjects who will subsequently phenoconvert. However, sensitivity and specificity are limited, and TCS does not seem to be suitable in the differential diagnosis of the different α-synucleinopathies that may develop with RBD progression.

Combining different imaging modalities might enhance accuracy of prognosis, which should be considered in future studies. Moreover, more longitudinal studies are warranted to validate the current findings.

Research agenda

1) To gain a more thorough understanding of RBD pathology and its association with neurodegenerative α-synucleinopathies.
2) To identify brain imaging markers enabling reliable prognoses on the course of the disease.
3) To provide recommendations for the application of currently available neuroimaging modalities to monitor disease progression and risk of subsequent phenoconversion.
4) To highlight the need for further research, especially longitudinal studies, verifying the current findings and giving deeper insights into RBD pathogenesis as it progresses towards a neurodegenerative disorder.

Conflicts of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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* The most important references are denoted by an asterisk.

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