

Progress in the Study of Imaging Biomarkers of Parkinson's Disease with REM Sleep Behaviour Disorder

Yaqin Huang, Xuan Zhang, Li Ma, Rong Xue*

Department of Neurology, General Hospital of Tianjin Medical University, Tianjin
Email: 15032250163@163.com, *xuerong1403@126.com

Received: Mar. 31st, 2020; accepted: Apr. 14th, 2020; published: Apr. 21st, 2020

Abstract

REM sleep behaviour disorder (RBD) is a complex behavior disorder associated with dreams that occur during rapid eye movement (REM). Idiopathic RBD (iRBD) is closely related to neurodegeneration such as Parkinson's disease, Louis dementia, multiple atrophy systems and so on. Among of them, Parkinson's disease is the most common. iRBD is a precursor to neurodegeneration. It's particularly important to discover and intervene in neurodegeneration early. Many studies have focused on the biomarkers of RBD-related neurodegeneration, in which imaging techniques have become a hot topic for their objectivity and rapid progress. The aim of this paper is to review the recent advances in imaging-related Parkinson's disease precursor biomarkers.

Keywords

REM Sleep Behaviour Disorder (RBD), Parkinson Disease, Imaging Biomarkers

快速眼动睡眠期行为障碍相关的帕金森病的影像学生物标志研究进展

黄雅琴, 张 轩, 马 莉, 薛 蓉*

天津医科大学总医院神经内科, 天津
Email: 15032250163@163.com, *xuerong1403@126.com

收稿日期: 2020年3月31日; 录用日期: 2020年4月14日; 发布日期: 2020年4月21日

*通讯作者。

文章引用: 黄雅琴, 张轩, 马莉, 薛蓉. 快速眼动睡眠期行为障碍相关的帕金森病的影像学生物标志研究进展[J]. 国际神经精神科学杂志, 2020, 9(2): 13-19. DOI: 10.12677/ijpn.2020.92002

摘要

快速眼动睡眠期行为障碍(REM sleep behaviour disorder, RBD)是一种发生在快速眼动期(rapid eye movement, REM)的一种与梦境相关的复杂行为障碍, 特发性快速眼动睡眠期行为障碍(idiopathic RBD, iRBD)与神经变性病如帕金森病(Parkinson's disease, PD)、路易体痴呆(dementia with Lewy bodies, DLB)、多系统萎缩(multiple system atrophy, MSA)等密切相关, 其中帕金森病最常见。iRBD是神经变性病的前驱症状。尽早发现并干预神经变性病显得尤为重要。当前许多研究致力于寻找RBD相关的神经变性病的生物学标志, 其中影像学方面的技术因其客观性和快速进展性而成为研究热点。本文旨在将当前的影像学相关的帕金森病前驱症状生物学标志研究进展做一综述。

关键词

快速眼动睡眠期行为障碍, 帕金森病, 影像学生物标志物

Copyright © 2020 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

快速眼动睡眠期行为障碍(REM sleep behaviour disorder, RBD)是一种发生在快速眼动期(rapid eye movement, REM)的一种与梦境相关的复杂行为障碍, 患者于睡梦中可出现梦呓、肢体活动等梦境演绎行为, 梦境多与暴力相关, 女性患者在梦境中常为暴力受害者, 患者常因这些复杂行为而伤害自己或床伴, 这些行为通常在睡眠开始后 2 小时开始, 主要发生在夜间的第二部分, 该部分 REM 睡眠期最长[1], 与 NREM 期异态睡眠不同, 患者常对夜间发生的行为不知情, 且往往不能在出现这些行为后马上醒来, 除非有较为严重的创伤[2]。多导睡眠监测(PSG)特征为 REM 期肌肉失迟缓[3] [4]。RBD 分为特发性 RBD (idiopathic RBD, iRBD)和继发性 RBD, iRBD 是指无明确原因的 RBD。全球范围内经问卷筛查得出的临床 iRBD 发病率为 3%~10% [1]。韩国的一项研究显示, 经 v-PSG 确诊的 iRBD 发病率为 1.15% [5]; 越来越多的研究表明, iRBD 与神经变性病如帕金森病(Parkinson's disease, PD)、路易体痴呆(dementia with Lewy bodies, DLB)、多系统萎缩(multiple system atrophy, MSA)等密切相关。随访研究发现, 10 年 iRBD 患者神经变性病转化率大于 90% [6]。许多学者认为, iRBD 是神经变性病的前驱症状。早期发现、识别神经变性病, 并早期干预是十分重要的。基于 iRBD 与神经变性病的密切关系, 目前越来越多的研究致力于寻找 RBD 相关的帕金森病的生物学标志, 其中影像学方面的技术因其客观性和快速进展性而成为研究热点。本文旨在将当前的影像学相关的帕金森病前驱症状生物学标志物研究进展做一综述。

2. 结构影像

2.1. 磁共振成像技术(MRI)

结构性磁共振成像技术中在 iRBD 研究中应用较多的是弥散张量成像(diffusion tensor imaging, DTI)和基于体素的形态学测量(voxel based morphometry, VBM), DTI 是利用水分子的弥散各向异性进行成像, 可用于评估脑白质纤维的结构完整性, 已经广泛应用于 PD 白质微结构异常的研究中, 多有阳性发现, 尤其在黑质, 并且在帕金森病和其他帕金森综合征的鉴别上有望成为一有效的生物指标, 但在 iRBD 中

的研究多无发现明确异常[7]。VBM 是一项用于测量脑部白质及灰质结构完整性的影像学分析技术,多用于脑灰质微结构异常的研究,研究发现 iRBD 患者额叶、前扣带回、丘脑、桥脑或海马等部位灰质体积缩小[8] [9] [10],但 Scherfler 等的研究[11]却发现海马体积增加。所以,结构性磁共振技术对于 iRBD 研究并无特异性,目前尚不支持其作为评估 iRBD 神经变性病转化风险评估的有效手段。

铁代谢相关的核磁共振技术有横向弛豫率(R_2)、表观横向弛豫率(R_2^*)、场强依赖性横向弛豫率(R_2')、有效横向弛豫时间(T_2^*)、磁敏感加权成像(SWI)、定量磁敏感图技术(QSM)等,其中 QSM 是根据 SWI 序列进一步分析计算得到的新技术,根据相位信息定量出大脑不同组织中脑铁磁化率的差异。该技术能精确表现各个脑区的铁含量,存在较高的组织敏感度。已经成功应用于帕金森病等许多神经退行性疾病的研究中。Yuto Uchida 等的研究发现 PD 伴轻度认知障碍(MCI)患者(PD-MCI)在尾状核头、海马旁回、杏仁核、前额叶的 QSM 值高于不伴 MCI 的 PD 患者(PD-CN),而 PD-CN 在黑质、苍白球、壳核的 QSM 值高于正常对照组,并且发现壳核及苍白球的 QSM 值与 MDS-UPDRS 评分呈相关性,尾状核头的 QSM 值与 MOCA 评分呈显著相关性[12]。另一项研究指出,黑质、苍白球、红核等部位的 QSM 值与 PD 病程呈显著正相关性[13]。特发性快速眼动睡眠期行为障碍患者与健康对照组相比,双侧黑质中铁升高。帕金森病患者比健康对照组双侧黑质、苍白球、左红核铁沉积增加,与 iRBD 患者相比,双侧黑质铁沉积增加明显,iRBD 患者左侧黑质铁的异常沉积与病程呈正相关[14]。

2.2. 经颅黑质超声

有研究发现 iRBD 患者黑质超声回声高于正常对照组,而低于 PD 组,提示黑质高回声可能是 iRBD 患者帕金森病的临床前表现[15]。然而,另外一项纳入 55 例 iRBD 患者,随访 5 年的前瞻性研究发现黑质回声的大小不随 iRBD 病情的进展而变化,且与 iRBD 转化为神经变性病无明确相关性[16]。同样,一项纳入 43 例 iRBD 患者,随访 2.5 年的前瞻性研究发现,结合黑质高回声及 123I-FP-CIT SPECT 预测突触核蛋白病转变的敏感性为 100%,特异性为 55% [17]。因此,单纯的黑质高回声并不能作为 iRBD 转化为突触核蛋白病的明确生物学指标。

3. 功能影像

3.1. 核素显像技术

关于正电子发射断层扫描(PET)和单光子发射断层扫描(SPECT)在 RBD 中应用已有大量研究,主要分为脑内多巴胺能显像、脑血流灌注显像、脑代谢显像以及小胶质细胞显像等。

3.1.1. 脑内多巴胺能显像

脑内多巴胺显像又分为突触前多巴胺能及突触后膜多巴胺能显像。突触后膜多巴胺显像的诸多研究结果不一,多数研究未发现突触后膜示踪剂的摄取与疾病呈相关性。突触前膜多巴胺能 PET 常用的示踪剂是[18F]FDOPA (L-3,4-dihydroxy-6-[18F]fluorophenylalanine)或[18F]FMT (6-[18F]fluoro-1-m-tyrosine),它可测定左旋多巴转化为多巴胺的能力。突触前膜多巴胺能 SPECT 检查最常用的示踪剂是 123I-FP-CIT(N-(3-fluoropropyl)-2b-carbomethoxy-3b-(4-[123I]iodophenyl)nortropine),其原理是测量多巴胺转运体(dopamine transporter, DAT)的密度[18],已有大量研究证实帕金森病患者纹状体多巴胺转运体减少。有研究指出,纹状体多巴胺能的不足与 RBD 的轻度运动障碍相关[19],亚临床 RBD (即 PSG 证实 REM 肌肉失迟缓,而无明显夜间睡眠行为障碍)到有临床症状的 RBD,再到帕金森病患者,纹状体突触前膜的多巴胺转运体逐渐减少,且均低于正常对照组[20]。一项为期 3 年的前瞻性研究发现,RBD 患者双侧壳核和尾状核的多巴胺转运体逐渐减少,且发现在基线时多巴胺转运体密度最低的 3 位患者第 3 年转化成了帕金森病[21]。但是由于相关研究的样本量都不大,所以 SPECT 是否可作为评估 iRBD 转变成

帕金森病的风险评估手段还需要更大样本量的研究来佐证。

3.1.2. 核素脑代谢显像

脑代谢显像使用较多的示踪剂是 18F-氟脱氧葡萄糖(18F-FDG)-PET。目前, PD 相关脑代谢模式(Parkinson's disease-related pattern, PDRP)已被证实可以用来评估疾病的进展和对治疗的反应[22]。PRDP 也被认为是 PD 早期诊断的可靠生物学标志。PDRP 的特点是丘脑、苍白球、桥脑和初级运动皮层表现为高代谢, 侧前运动区和顶叶后区的代谢相对减少[23]。有研究用 18F-FDG-PET 探究了 iRBD 的代谢网络, 发现 RBD 相关脑代谢模式(RBD-related covariance pattern, RBDRP)特征是桥脑、丘脑、内侧额叶、感觉运动区、海马、颞上和下回以及小脑后部的活动增加, 枕叶和颞上区域的活动减少。揭示了 iRBD 与帕金森病的代谢显像在丘脑、感觉运动区、脑桥等部位存在不同程度的重叠[24]。RBDRP 或可成为评估 iRBD 转化为神经变性病尤其是帕金森病风险的有效生物学标志。

3.1.3. 脑血流显像

脑血流量(cerebral blood flow, CBF)指动脉血到脑组织毛细血管的速度。早已发现 CBF 与脑氧流量和脑葡萄糖消耗水平密切相关[25]。SPECT 技术中较常用是试剂有 ^{99m}Tc -Ethylene Cysteinate Dimer (^{99m}Tc -ECD)。研究发现, 与对照组相比, RBD 患者在额叶区域表现为低灌注。RBD 伴轻度认知障碍患者较不伴轻度认知障碍患者在枕叶、颞部和顶叶部分区域表现出皮质低灌注, 且二者均有海马及海马旁回的高灌注[26]。其他许多研究也指出 iRBD 患者皮层部分脑区如额叶、枕叶等低灌注, 海马等皮层下高灌注, 这与前文所述的 PDRP 模式中脑代谢特征相似, 且与 PD 和 BLD 患者局部脑血流量异常改变相似[27][28]。综上, 基于核素显像技术的脑血流灌注对于支持 iRBD 为神经变性病前驱症状及认知障碍的评估具有重要意义, 但其对于 iRBD 发展方向的预测还需要更多的纵向随访研究来探究, 然而, 由于核素显像检查的过程复杂、试剂高辐射、频繁抽血、费用高等缺点, 大样本纵向随访研究的开展存在困难。

3.1.4. 小胶质细胞显像

小胶质细胞显像中最常用的放射物示踪剂为 11C-PK11195, 它是转位蛋白 18 kDa (translocator protein 18 kDa, TSPO 18 kDa)配体, TSPO 表达于线粒体外膜, 参与调控线粒体功能、氧化应激反应、类固醇合成、免疫炎症反应等功能, 被看作是神经炎症的分子标志物。已经在阿尔茨海默病、帕金森病、多发性硬化等疾病中证实了 TSPO 表达增高[29]。Stokholm 等人的研究发现 iRBD 患者黑质的小胶质细胞表达明显增高, 且 18F-DOPA PET 检测到的壳核多巴胺能丢失相匹配[30]。神经炎症在神经变性病中的作用机制还待进一步探讨, 小胶质细胞显像能否作为评估 iRBD 有效生物学标志还需更多样本量足够的研究证实。

3.2. 磁共振脑血流显像

相比于核素显像技术对脑血流量(cerebral blood flow, CBF)的测量, ASL 是以动脉血流内的水分子为内源性造影剂成像, 可以定量反应局部脑组织血流灌注量, 且具有可操作性强、可重复性强、无需试剂、无辐射、价格低廉等优势, 目前已经在神经变性病、脑肿瘤、脑血管病、癫痫、脑炎等方面展开诸多研究。一项研究发现阿尔茨海默症(AD)患者脑血流灌注和脑葡萄糖代谢呈现一致性[31]。相比于健康人, 帕金森病患者后枕叶皮质、前叶和楔形以及额中回的脑血流灌注减少[32]。一项纳入 15 例 iRBD 患者和 20 例健康对照组的研究发现, iRBD 组 MOCA 评分、额叶和岛叶血流灌注低于对照组[33]。目前, 基于 ASL 技术的关于 iRBD 患者脑灌注情况的研究尚不多, 但由于该项技术的诸多优点, 相信未来将有等多的研究开展起来。

3.3. 功能性磁共振成像技术

功能性磁共振成像技术(functional magnetic resonance imaging, fMRI), 它是利用血氧水平依赖(the blood oxygen level-dependent, BOLD)信号的变化来识别神经元活动增加或减少的区域[34], 其中用于脑功能连接研究的称为(Resting-state functional connectivity functional MRI, fcMRI), 研究发现 PD 病患者丘脑、中脑、桥脑和小脑的纹状体相关性明显较低[35]。同样在 iRBD 的研究中, 发现了 iRBD 患者黑质和纹状体之间的功能连接发生改变, 且左侧半球更显著, 这与 PD 患者左侧半球黑质纹状体功能损害更多见表现了一致性, 提示该项技术具有 iRBD 发展为 PD 的预测意义[36], 但目前功能性成像技术应用于 iRBD 患者的研究较少, 且缺乏纵向随访研究的数据支持, 尚不能得出 fMRI 可作为神经变性病尤其是帕金森病可靠预测指标的结论, 需要更多大样本量、纵向观察的研究来扩充数据。

综上, 目前对于 RBD 作为神经变性病尤其是帕金森病前驱症状的相关生物学标志的影像学研究包括结构影像、功能影像。突触前膜多巴胺能显像、脑代谢显像等核素显像技术在 iRBD 与 PD 相关性的研究上有了诸多令人鼓舞的发现, 但核素显像技术因受其高成本、高辐射、临床接受度低等影响, 临床运用受到限制。基于核素显像技术和核磁共振技术的脑血流显像有了较为一致的发现即 iRBD 患者皮层低灌注、皮层下高灌注[27], 脑血流灌注的异常被认为与神经变性病的认知障碍相关[37], 脑血流显像中 ASL 技术因易操作、无辐射、费用低凸显了其优越性, 虽其预测价值尚不十分明确, 但长期随访并结合认知心理评估以观察其认知减退进展是可行的。小胶质细胞显像研究神经变性病发病机制关注到神经炎症机制, 但由于神经炎症机制在神经变性病的发病机制中的作用尚不明确, 故 iRBD 的小胶质细胞显像研究是近几年才出现的热点, 研究数据目前尚少, 需更多的大样本量、纵向观察等研究来证实其预测意义。目前没有一项影像学检查可以单独作为 iRBD 发展为帕金森病风险预测的指标, 但基于上述诸多可喜的研究结果, 将影像学检查与其他多项生物学标志如嗅觉减退、自主神经功能紊乱、认知减退、轻微运动障碍等相结合[38], 或许可以为 iRBD 患者病程的监测及神经变性病尤其是帕金森病的转化风险提供更准确的客观支持。

参考文献

- [1] Dauvilliers, Y., Schenck, C.H., Postuma, R.B., Iranzo, A., Luppi, P.H., Plazzi, G., Montplaisir, J. and Boeve, B. (2018) REM Sleep Behaviour Disorder. *Nature Reviews Disease Primers*, **4**, 19. <https://doi.org/10.1038/s41572-018-0016-5>
- [2] Castelnovo, A., Lopez, R., Proserpio, P., Nobili, L. and Dauvilliers, Y. (2018) NREM Sleep Parasomnias as Disorders of Sleep-State Dissociation. *Nature Reviews Neurology*, **14**, 470-481. <https://doi.org/10.1038/s41582-018-0030-y>
- [3] Arnaldi, D., Antelmi, E., St Louis, E.K., Postuma, R.B. and Arnulf, I. (2017) Idiopathic REM Sleep Behavior Disorder and Neurodegenerative Risk: To Tell or Not to Tell to the Patient? How to Minimize the Risk? *Sleep Medicine Reviews*, **36**, 82-95. <https://doi.org/10.1016/j.smrv.2016.11.002>
- [4] Bodkin, C.L. and Schenck, C.H. (2009) Rapid Eye Movement Sleep Behavior Disorder in Women: Relevance to General and Specialty Medical Practice. *Journal of Women's Health*, **18**, 1955-1963. <https://doi.org/10.1089/jwh.2008.1348>
- [5] Kang, S.H., Yoon, I.Y., Lee, S.D., Han, J.W., Kim, T.H. and Kim, K.W. (2013) REM Sleep Behavior Disorder in the Korean Elderly Population: Prevalence and Clinical Characteristics. *Sleep*, **36**, 1147-1152. <https://doi.org/10.5665/sleep.2874>
- [6] Iranzo, A., Tolosa, E., Gelpi, E., Molinuevo, J.L., Valldeoriola, F., Serradell, M., Sanchez-Valle, R., Vilaseca, I., Lomeña, F., Vilas, D., Lladó, A., Gaig, C. and Santamaria, J. (2013) Neurodegenerative Disease Status and Post-Mortem Pathology in Idiopathic Rapid-Eye-Movement Sleep Behaviour Disorder: An Observational Cohort Study. *The Lancet Neurology*, **12**, 443-453. [https://doi.org/10.1016/S1474-4422\(13\)70056-5](https://doi.org/10.1016/S1474-4422(13)70056-5)
- [7] Rahayel, S., Montplaisir, J., Monchi, O., Bedetti, C., Postuma, R.B., Brambati, S., Carrier, J., Joubert, S., Latreille, V., Jubault, T. and Gagnon, J.F. (2015) Patterns of Cortical Thinning in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. *Movement Disorders*, **30**, 680-687. <https://doi.org/10.1002/mds.25820>
- [8] Rahayel, S., Postuma, R.B., Montplaisir, J., Bedetti, C., Brambati, S., Carrier, J., Monchi, O., Bourgouin, P.A., Gaubert,

- M. and Gagnon, J.F. (2018) Abnormal Gray Matter Shape, Thickness, and Volume in the Motor Cortico-Subcortical Loop in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: Association with Clinical and Motor Features. *Cerebral Cortex*, **28**, 658-671. <https://doi.org/10.1093/cercor/bhx137>
- [9] Pyatigorskaya, N., Gaurav, R., Arnaldi, D., Leu-Semenescu, S., Yahia-Cherif, L., Valabregue, R., Vidailhet, M., Arnulf, I. and Lehericy, S. (2017) Magnetic Resonance Imaging Biomarkers to Assess Substantia Nigra Damage in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. *Sleep*, **40**. <https://doi.org/10.1093/sleep/zsx149>
- [10] Hanyu, H., Inoue, Y., Sakurai, H., Kanetaka, H., Nakamura, M., Miyamoto, T., Sasai, T. and Iwamoto, T. (2012) Voxel-Based Magnetic Resonance Imaging Study of Structural Brain Changes in Patients with Idiopathic REM Sleep Behavior Disorder. *Parkinsonism & Related Disorders*, **18**, 136-139. <https://doi.org/10.1016/j.parkreldis.2011.08.023>
- [11] Scherfler, C., Frauscher, B., Schocke, M., Iranzo, A., Gschliesser, V., Seppi, K., Santamaria, J., Tolosa, E., Hogl, B. and Poewe, W. (2011) White and Gray Matter Abnormalities in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: A Diffusion-Tensor Imaging and Voxel-Based Morphometry Study. *Annals of Neurology*, **69**, 400-407. <https://doi.org/10.1002/ana.22245>
- [12] Uchida, Y., Kan, H., Sakurai, K., Arai, N., Kato, D., Kawashima, S., Ueki, Y. and Matsukawa, N. (2019) Voxel-Based Quantitative Susceptibility Mapping in Parkinson's Disease with Mild Cognitive Impairment. *Movement Disorders*, **34**, 1164-1173. <https://doi.org/10.1002/mds.27717>
- [13] Shahmaei, V., Faeghi, F., Mohammdbegi, A., Hashemi, H. and Ashrafi, F. (2019) Evaluation of Iron Deposition in Brain Basal Ganglia of Patients with Parkinson's Disease Using Quantitative Susceptibility Mapping. *European Journal of Radiology Open*, **6**, 169-174. <https://doi.org/10.1016/j.ejro.2019.04.005>
- [14] Sun, J., Lai, Z., Ma, J., Gao, L., Chen, M., Chen, J., Fang, J., Fan, Y., Bao, Y., Zhang, D., Chan, P., Yang, Q., Ye, C., Wu, T. and Ma, T. (2019) Quantitative Evaluation of Iron Content in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. *Movement Disorders*, **35**, 478-485. <https://doi.org/10.1002/mds.27929>
- [15] Shin, H.Y., Joo, E.Y., Kim, S.T., Dhong, H.J. and Cho, J.W. (2013) Comparison Study of Olfactory Function and Substantia Nigra Hyperechogenicity in Idiopathic REM Sleep Behavior Disorder, Parkinson's Disease and Normal Control. *Neurological Sciences*, **34**, 935-940. <https://doi.org/10.1007/s10072-012-1164-0>
- [16] Iranzo, A., Stockner, H., Serradell, M., Seppi, K., Valldeoriola, F., Frauscher, B., Molinuevo, J.L., Vilaseca, I., Mitterling, T., Gaig, C., Vilas, D., Santamaria, J., Hogl, B., Tolosa, E. and Poewe, W. (2014) Five-Year Follow-Up of Substantia Nigra Echogenicity in Idiopathic REM Sleep Behavior Disorder. *Movement Disorders*, **29**, 1774-1780. <https://doi.org/10.1002/mds.26055>
- [17] Iranzo, A., Lomeña, F., Stockner, H., Valldeoriola, F., Vilaseca, I., Salamero, M., Molinuevo, J.L., Serradell, M., Duch, J., Pavia, J., Gallego, J., Seppi, K., Högl, B., Tolosa, E., Poewe, W. and Santamaria, J. (2010) Decreased Striatal Dopamine Transporter Uptake and Substantia Nigra Hyperechogenicity as Risk Markers of Synucleinopathy in Patients with Idiopathic Rapid-Eye-Movement Sleep Behaviour Disorder: A Prospective Study. *The Lancet Neurology*, **9**, 1070-1077. [https://doi.org/10.1016/S1474-4422\(10\)70216-7](https://doi.org/10.1016/S1474-4422(10)70216-7)
- [18] Shen, L.H., Liao, M.H. and Tseng, Y.C. (2012) Recent Advances in Imaging of Dopaminergic Neurons for Evaluation of Neuropsychiatric Disorders. *Journal of Biomedicine and Biotechnology*, **2012**, Article ID: 259349. <https://doi.org/10.1155/2012/259349>
- [19] Rupperecht, S., Walther, B., Gudziol, H., Steenbeck, J., Freesmeyer, M., Witte, O.W., Gunther, A. and Schwab, M. (2013) Clinical Markers of Early Nigrostriatal Neurodegeneration in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. *Sleep Medicine*, **14**, 1064-1070. <https://doi.org/10.1016/j.sleep.2013.06.008>
- [20] Eisensehr, I., et al. (2003) Increased Muscle Activity during Rapid Eye Movement Sleep Correlates with Decrease of Striatal Presynaptic Dopamine Transporters. IPT and IBZM SPECT Imaging in Subclinical and Clinically Manifest Idiopathic REM Sleep Behavior Disorder, Parkinson's Disease, and Controls. *Sleep*, **26**, 507-512. <https://doi.org/10.1093/sleep/26.5.507>
- [21] Iranzo, A., Valldeoriola, F., Lomena, F., Molinuevo, J.L., Serradell, M., Salamero, M., Cot, A., Ros, D., Pavia, J., Santamaria, J. and Tolosa, E. (2011) Serial Dopamine Transporter Imaging of Nigrostriatal Function in Patients with Idiopathic Rapid-Eye-Movement Sleep Behaviour Disorder: A Prospective Study. *The Lancet Neurology*, **10**, 797-805. [https://doi.org/10.1016/S1474-4422\(11\)70152-1](https://doi.org/10.1016/S1474-4422(11)70152-1)
- [22] Ma, Y., Tang, C., Spetsieris, P.G., Dhawan, V. and Eidelberg, D. (2007) Abnormal Metabolic Network Activity in Parkinson's Disease: Test-Retest Reproducibility. *Journal of Cerebral Blood Flow & Metabolism*, **27**, 597-605. <https://doi.org/10.1038/sj.jcbfm.9600358>
- [23] Eidelberg, D. (2009) Metabolic Brain Networks in Neurodegenerative Disorders: A Functional Imaging Approach. *Trends in Neurosciences*, **32**, 548-557. <https://doi.org/10.1016/j.tins.2009.06.003>
- [24] Wu, P., Yu, H., Peng, S., Dauvilliers, Y., Wang, J., Ge, J., Zhang, H., Eidelberg, D., Ma, Y. and Zuo, C. (2014) Consistent Abnormalities in Metabolic Network Activity in Idiopathic Rapid Eye Movement Sleep Behaviour Disorder. *Brain*, **137**, 3122-3128. <https://doi.org/10.1093/brain/awu290>

- [25] Sokoloff, L. (1977) Relation between Physiological Function and Energy Metabolism in the Central Nervous System. *Journal of Neurochemistry*, **29**, 13-26. <https://doi.org/10.1111/j.1471-4159.1977.tb03919.x>
- [26] Vendette, M., Montplaisir, J., Gosselin, N., Soucy, J.P., Postuma, R.B., Dang-Vu, T.T. and Gagnon, J.F. (2012) Brain Perfusion Anomalies in Rapid Eye Movement Sleep Behavior Disorder with Mild Cognitive Impairment. *Movement Disorders*, **27**, 1255-1261. <https://doi.org/10.1002/mds.25034>
- [27] Hanyu, H., Inoue, Y., Sakurai, H., Kanetaka, H., Nakamura, M., Miyamoto, T., Sasai, T. and Iwamoto, T. (2011) Regional Cerebral Blood Flow Changes in Patients with Idiopathic REM Sleep Behavior Disorder. *European Journal of Neurology*, **18**, 784-788. <https://doi.org/10.1111/j.1468-1331.2010.03283.x>
- [28] Vendette, M., Gagnon, J.F., Soucy, J.P., Gosselin, N., Postuma, R.B., Tuineag, M., Godin, I. and Montplaisir, J. (2011) Brain Perfusion and Markers of Neurodegeneration in Rapid Eye Movement Sleep Behavior Disorder. *Movement Disorders*, **26**, 1717-1724. <https://doi.org/10.1002/mds.23721>
- [29] Xu, J., et al. (2019) Translocator Protein in Late Stage Alzheimer's Disease and Dementia with Lewy Bodies Brains. *Annals of Clinical and Translational Neurology*, **6**, 1423-1434.
- [30] Stokholm, M.G., Iranzo, A., Østergaard, K., Serradell, M., Otto, M., Svendsen, K.B., Garrido, A., Vilas, D., Borghammer, P., Santamaria, J., Møller, A., Gaig, C., Brooks, D.J., Tolosa, E. and Pavese, N. (2017) Assessment of Neuroinflammation in Patients with Idiopathic Rapid-Eye-Movement Sleep Behaviour Disorder: A Case-Control Study. *The Lancet Neurology*, **16**, 789-796. [https://doi.org/10.1016/S1474-4422\(17\)30173-4](https://doi.org/10.1016/S1474-4422(17)30173-4)
- [31] Chen, Y., Wolk, D.A., Reddin, J.S., Korczykowski, M., Martinez, P.M., Musiek, E.S., Newberg, A.B., Julin, P., Arnold, S.E., Greenberg, J.H. and Detre, J.A. (2011) Voxel-Level Comparison of Arterial Spin-Labeled Perfusion MRI and FDG-PET in Alzheimer Disease. *Neurology*, **77**, 1977-1985. <https://doi.org/10.1212/WNL.0b013e31823a0ef7>
- [32] Melzer, T.R., Watts, R., MacAskill, M.R., Pearson, J.F., Rueger, S., Pitcher, T.L., Livingston, L., Graham, C., Keenan, R., Shankaranarayanan, A., Alsup, D.C., Dalrymple-Alford, J.C. and Anderson, T.J. (2011) Arterial Spin Labelling Reveals an Abnormal Cerebral Perfusion Pattern in Parkinson's Disease. *Brain*, **134**, 845-855. <https://doi.org/10.1093/brain/awq377>
- [33] Chen, Y., Fan, C., Yang, W., Nie, K., Wu, X., Yang, Y., Yang, Y., Wang, L., Zhang, Y. and Huang, B. (2019) Cortical Hypoperfusion in Patients with Idiopathic Rapid Eye Movement Sleep Behavior Disorder Detected with Arterial Spin-Labeled Perfusion MRI. *Neurological Sciences*. <https://doi.org/10.1007/s10072-019-04118-5>
- [34] Logothetis, N.K. (2003) The Underpinnings of the BOLD Functional Magnetic Resonance Imaging Signal. *Journal of Neuroscience*, **23**, 3963-3971. <https://doi.org/10.1523/JNEUROSCI.23-10-03963.2003>
- [35] Hacker, C.D., Perlmutter, J.S., Criswell, S.R., Ances, B.M. and Snyder, A.Z. (2012) Resting State Functional Connectivity of the Striatum in Parkinson's Disease. *Brain*, **135**, 3699-3711. <https://doi.org/10.1093/brain/aws281>
- [36] Ellmore, T.M., Castriotta, R.J., Hendley, K.L., Aalbers, B.M., Furr-Stimming, E., Hood, A.J., Suescun, J., Beurlot, M.R., Hendley, R.T. and Schiess, M.C. (2013) Altered Nigrostriatal and Nigrocortical Functional Connectivity in Rapid Eye Movement Sleep Behavior Disorder. *Sleep*, **36**, 1885-1892. <https://doi.org/10.5665/sleep.3222>
- [37] Nobili, F., Abbruzzese, G., Morbelli, S., Marchese, R., Girtler, N., Dessi, B., Brugnolo, A., Canepa, C., Drosos, G.C., Sambucetti, G. and Rodriguez, G. (2009) Amnesic Mild Cognitive Impairment in Parkinson's Disease: A Brain Perfusion SPECT Study. *Movement Disorders*, **24**, 414-421. <https://doi.org/10.1002/mds.22381>
- [38] Postuma, R.B., Iranzo, A., Hu, M., Hogl, B., Boeve, B.F., Manni, R., Oertel, W.H., Arnulf, I., Ferini-Strambi, L., Puligheddu, M., Antelmi, E., Cochen De Cock, V., Arnaldi, D., Mollenhauer, B., Videnovic, A., Sonka, K., Jung, K.Y., Kunz, D., Dauvilliers, Y., Provini, F., Lewis, S.J., Buskova, J., Pavlova, M., Heidebreder, A., Montplaisir, J.Y., Santamaria, J., Barber, T.R., Stefani, A., St Louis, E.K., Terzaghi, M., Janzen, A., Leu-Semenescu, S., Plazzi, G., Nobili, F., Sixel-Doering, F., Dusek, P., Bes, F., Cortelli, P., Ehgoetz Martens, K., Gagnon, J.F., Gaig, C., Zucconi, M., Trenkwalder, C., Gan-Or, Z., Lo, C., Rolinski, M., Mahlknecht, P., Holzknecht, E., Boeve, A.R., Teigen, L.N., Toscano, G., Mayer, G., Morbelli, S., Dawson, B. and Pelletier, A. (2019) Risk and Predictors of Dementia and Parkinsonism in Idiopathic REM Sleep Behaviour Disorder: A Multicentre Study. *Brain*, **142**, 744-759. <https://doi.org/10.1093/brain/awz030>