综 述

定量磁化率成像在帕金森病研究进展*

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【摘要】帕金森病是世界上仅次于阿尔兹海默症的严重运动功能障碍疾病，其临床表现包括运动症状和非运动症状，目前其发病机制尚未明确，但通常认为黑质铁沉积在帕金森病中起到重要作用，目前对于帕金森病的诊断仍依靠临床症状，影像学方面仍欠缺相关诊断标准，近年来，定量磁化率(quantitative magnetic susceptibility，QSM)成像因其在定量体内铁沉积含量方面的独特优势已逐渐运用于帕金森病的诊断及鉴别诊断价值的研究。本文针对QSM成像在帕金森病的相关研究进展进行综述。

【关键词】帕金森病；定量磁化率成像；磁共振成像
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Research Progress of Quantitative Susceptibility Imaging in Parkinson's Disease*

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ABSTRACT
Parkinson's disease is a serious motor dysfunction disease second only to Alzheimer's disease in the world. Its clinical manifestations include motor symptoms and non-motor symptoms. At present, its pathogenesis is not clear, but it is generally believed that iron deposition in the nigra plays an important role in Parkinson's disease. quantitative magnetic susceptibility (QSM) imaging has been gradually applied to the diagnosis and differential diagnosis of Parkinson's disease due to its unique advantages in quantifying iron deposition content in the body. This article reviews the research progress of QSM imaging in Parkinson's disease.
Keywords: Parkinson's Disease; Quantitative Susceptibility Imaging; Magnetic Resonance Imaging

帕金森病是一种进行性退行性神经系统疾病，其临床症状除运动功能障碍外，还可伴发抑郁、幻觉和淡漠等非运动症状[1]，帕金森病发病率仅次于阿尔茨海默症，是世界上第二大神经退行性疾病，60岁以上的成年人约有2%患病，其发病率随年龄的增长呈上升趋势，80岁以上的人口中约有5%受到影响[2]。最新研究发现，男性患帕金森病的风险是女性的两倍，但女性患者病情进展更快且死亡率更高[3]。帕金森病的发病机制尚未明确，通常认为黑质铁沉积在帕金森病中起重要作用，目前，帕金森病的诊断仍主要基于临床表现，而在影像学检查中，多巴胺转运体的单电子成像(DAT SPECT)虽然可以用于帕金森病的辅助诊断，但是其价格高昂，并不适合临床常规使用，且DAT SPECT并不能用于帕金森病和非典型帕金森综合征的鉴别，而常规MRI虽对鉴别帕金森综合征和帕金森病有一定帮助，但帕金森病本身的MRI表现却并无特异性[4]。定量磁化率(quantitative magnetic susceptibility，QSM)成像作为新兴的铁沉积定量检测方法，近年来已得到不断完善和发展，目前QSM成像在广泛应用到如帕金森病等与铁沉积相关的神经退行性疾病的临床研究的同时，在临床医疗等方面也展现出越来越大的研究潜力[5-8]。本文就目前QSM技术在帕金森病MRI影像诊断、鉴别诊断及其临床应用中的研究进展进行综述。

1 QSM成像原理及优势

目前已成功应用到帕金森病患者上的铁沉积定量分析方法主要包括横向弛豫率成像(R2* mapping)与QSM成像。定量磁化率成像通过将组织器官置于MRI系统的强外磁场中时所感应到磁化率差异来生成图像对比度[9]，与传统R2*成像仅采集磁共振信号幅度信息不同，QSM成像能够同时采集磁共振信号的幅度信息和相位信息，相位信息中所包含的组织信息能够间接反映组织间磁化率的差异，而组织磁化率的差异有助于识别如钙化等抗磁性物质或者铁等顺磁性物质。同时，R2*成像与铁的空间分布有关，而QSM成像则不受铁的微观空间分布的影响[10]，因此，在定量铁沉积能力上QSM比传统R2*成像更具优势，国内外的相关研究结果也表明QSM在量化微量铁沉积方面的敏感度比R2*成像更高[11-12]。帕金森病的病理特征是黑质铁沉积增多并伴有神经元变性，帕金森病患者黑质致密部中铁含量的增加可引起氧化应激反应，进而可以通过改变蛋白质处理方式和引起线粒体功能障碍而导致神经退化[13]。黑质网状部的多巴胺能神经元中含有一种能够与铁大量结合的神经黑素，濒临死亡的神经元可以向细胞外环境释放神经黑素，这在促进帕金森病炎症进展的同时，还可导致神经元炎症和神经退化的自我循环[14-16]。运用QSM成像对异常黑质进行综合评估对早期帕金森病的诊断具有较高价值[17]，其中，黑质小体-1(nigrosome-1)已然成为研究特发性帕金森病的新的成像生物标志物[18-19]，QSM成像定量的磁化率值有望在未来成为研究帕金森病的生物学标记物。

2 铁沉积模式

QSM可以作为帕金森病严重程度的客观生物标志物，黑质体积与疾病早期的病程和运动严重程度密切相关[20]，通过对帕金森病患者铁积累分布模式进行研究，Takahashi等发现帕金森病患者铁沉积的位置与黑质致密部相匹配，即位于红核的腹外侧区和黑质网状部的背内侧[21]。此外，有学者通过对包含经颅超声和QSM的成人大脑多模式图谱进行分析发现帕金森病患者的经颅超声和QSM信号的增加沿着整个中脑轴线高度重叠，该结果在证实了铁在黑质致密部积聚的既定发现的同时，也提示帕金森病患者中脑边缘系统早期受累，而不仅仅是孤立的黑质纹状体多巴胺神经元的丢失[22]。Chen等的研究发现，不同临床亚型帕金森病患者中铁沉积模式不同，这提示我们铁调节可能与帕金森病临床亚型的病理生理学相关[23]，而将QSM技术与MRI功能成像相结合可以对不同帕金森

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表型进行分类[24]。此外，帕金森病患者黑质铁沉积的进行性模式与帕金森病的病程相一致，黑质中铁的含量与帕金森病患者的临床表现密切相关，运动障碍的帕金森病患者可能是帕金森病患者中受影响最严重的亚群，但其潜在机制仍有待进一步研究[25]。

3 认知改变

帕金森病患者通常伴有如认知功能减低、幻觉和精神症状、抑郁、焦虑、淡漠和多巴胺失调综合征等非运动症状，这提示铁沉积的增加可能损害其他脑区，有研究发现，基底外神经节系统中的铁含量与非运动症状密切相关，特别是对于存在睡眠问题和自主神经障碍的患者[26]。认知功能减低在帕金森病中很常见，Thomas等的研究发现认知表现与海马的变化有关，认知功能障碍的风险与顶叶和额叶皮质中铁含量的增加有关，其严重程度与壳核中铁水平的升高呈同步变化[27]。虽然帕金森病患者的认知功能与边缘结构铁蓄积相关，但目前仍缺乏追踪帕金森病认知变化的方法，边缘系统铁浓度在帕金森病发病机制中的作用、与认知和精神的关系以及作为临床生物标志物在临床试验中的潜力也仍有待进一步的纵向研究[28]。Uchida等通过研究发现帕金森病患者行为和认知障碍及多巴胺能缺陷与纹状体铁蓄积相关，且帕金森病患者的认知和嗅觉障碍与尾状核磁化率改变有关，磁化率值的增加在尾状核发生形态学改变出现之前便已出现，同时，帕金森病患者纹状体QSM值与多巴胺转运体呈负相关关系，这提示我们QSM具有作为辅助生物标志物的潜力，可以用于监测帕金森病患者的疾病状态，包括帕金森综合症和认知功能障碍[29]。但也有研究表明帕金森病患者非运动症状与深层核团铁沉积无关[30]，这提示我们在对帕金森病非运动症状进行神经影像学研究时应使用更加详细具体的临床工具，同时还应招募具有典型非运动症状的帕金森病患者。

4 影像组学

Li等通过构建QSM纹理特征来评估帕金森病患者黑质中铁沉积的空间差异，结果表明，QSM纹理特征不仅能区分帕金森病患者和正常志愿者，而且其效能明显优于基于R2*成像纹理特征分析，且二阶纹理特征在帕金森病患者的分类上比一阶纹理特征更准确、更灵敏[31]。同时，Xiao等将卷积神经网络和放射组学特征用于QSM图像的研究结果表明放射组学特征和卷积神经网络特征相辅相成，将放射组学特征与卷积神经网络特征相结合可以提高诊断的准确性[32]。目前，QSM成像在该领域的相关研究仍相对较少，仍有待进一步研究。

5 鉴别诊断

帕金森病常需与非典型帕金森综合征如进行性核上性麻痹(PSP)和多系统萎缩(MSA)等相鉴别，但仅凭传统影像上肉眼所见很难在早期对其进行鉴别诊断。定量磁化率成像的出现为评估退行性帕金森病的大脑结构提供了新的方法，定量磁化率成像不仅可以定量测定脑组织铁含量，还能在脑组织出现区域性萎缩之前清晰显示其显微结构。Sjöström等的相关研究表明，帕金森病与非典型帕金森综合征具有不同的脑铁积累模式[33]，Mazzucchi等研究发现红核、丘脑底核(STN)和黑质内侧部的QSM值在进行性核上性麻痹中更高，而在多系统萎缩中，壳核的铁沉积明显更高[34]，同时有研究表明，QSM图像上苍白球中的平均磁化率值可以为区分进行性核上性麻痹和帕金森病提供形态学指标[35]。Ito等通过将弥散峰度成像(DKI)和QSM进行联合来定量评估帕金森病、进行性核上性麻痹和多系统萎缩患者的脑干和基底节，结果发现QSM和DKI相结合能够以高灵敏度和特异度来区分帕金森病和非典型帕金森综合征[36]，这些研究结果表明QSM提供的铁沉积信息可以作为诊断和鉴别帕金森病的生物标志物。

6 临床应用

脑深部刺激(DBS)是目前改善帕金森病症状的主要方法，该技术可以有效控制运动体征、改善患者功能和提高患者生活质量，目前，针对帕金森病运动症状的治疗主要有两种不同的靶点：苍白球内侧核(GPI)和丘脑底核，DBS成功的关键在于准确放置刺激电极，与传统的T_2WI图像相比，QSM提供的组织对比度能够通过直接定位丘脑底核和苍白球靶点来治疗帕金森病，尤其是对于大脑深部核不对称的患者[37]。IDE等的研究表明，QSM可以通过区分苍白球外侧部和苍白球内侧部而在术中精准定位苍白球内侧核[38]。STN因其主要参与认知和运动功能的调节目前已成为DBS的主要靶点，然而，由于尺寸小，方向倾斜，解剖位置多变等原因，精确定位STN一直以来都相当困难，而高分辨率QSM尤其是亚毫米级QSM扫描则能够从周围组织及其亚区之间清楚地显示STN[39]，同时QSM可以用于在DBS术中直接定位STN[40]。QSM在准确描绘STN边界的同时，还能提供STN分区的功能信息，这不仅有助于实施DBS手术，更可以避免与DBS相关的不良副作用[41]。此外，STN的边界和QSM信号梯度与PD患者的运动障碍相关，这一发现可能有助于优化帕金森病患者的DBS治疗方式[42]。

7 小　结

QSM作为铁沉积定量成像技术，有望成为研究帕金森病的生物学标志物。但目前用于在定量体内铁含量方面仍有技术缺陷，如QSM信号可能受到诸如钙，脂质或髓鞘含量等非金属因子的影响，虽然这些影响与铁相比微不足道，但目前的QSM方法无法确定异常磁化率背后的化学结构，也无法反映确切的铁的类型，QSM所测量到的局部铁含量的增加只是疾病状态的标志，而与疾病的发病机制没有直接关系。帕金森病的发病机制仍不清楚，而现今的大多数研究仍是横断面的研究，仍需进一步的纵向研究来探讨铁沉积与帕金森病的关系。

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