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·综　述·

语音声学分析在帕金森病中的诊断价值*

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【摘要】 帕金森病临床诊疗的核心与挑战之一是如何在早期筛查识别帕金森病、如何在疾病进展期精准诊断帕金森病。帕金森病患者常出现语言障碍，即语音障碍。随着技术的发展，声学分析技术为语音评估提供了诸多客观量化的指标，也进而使得利用语音声学分析实现帕金森病的早期识别与精准诊断成为可能。本文旨在梳理帕金森病语音障碍声学分析相关研究进展，首先引入目前帕金森病语音障碍评估中常用的声学指标；并依次介绍语音声学分析在精准诊断、早期筛查及鉴别诊断的价值，同时指出目前研究缺陷及展望，以期提高对帕金森病语音声学分析及其潜在诊断价值的认识。

【关键词】 帕金森病　语音障碍　声学分析

Diagnostic Value of Speech Acoustic Analysis in Parkinson's Disease

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【**Abstract**】 Screening for and identifying patients with Parkinson's disease (PD) at an early stage and forming accurate diagnosis of PD during the course of the progression of the disease are of essential importance but still remain challenging for the clinical diagnosis and treatment of PD. One of the common clinical manifestations of PD is speech impairment, or voice impairment. Thanks to the recent advances in the field of acoustic analysis, a large number of acoustic parameters have been proposed for evaluating speech impairment quantitatively. Early identification and accurate diagnosis of PD was henceforth made possible through the application of speech acoustic analysis. Herein, we summarized the latest research findings on the application of acoustic analysis in PD diagnosis. We reported some acoustic parameters commonly used in the evaluation of voice impairment in PD patients. Then, we presented the diagnostic value of acoustic analysis in developing accurate diagnosis, early screening and differential diagnosis. Furthermore, we discussed the drawbacks and prospects of current studies, intending to enhance understanding of acoustic analysis of PD patients and its potential diagnostic values.

【**Key words**】 Parkinson's disease　Speech impairment　Acoustic analysis

帕金森病（Parkinson's disease, PD）是一种常见的运动障碍性疾病，主要临床特征包括随意运动减少、动作缓慢、肌强直、静止性震颤等。该疾病会导致患者日常生活能力受损，生活质量严重下降；加之当今社会老年化的趋势以及其疾病高发性的特点，PD对社会造成了巨大的疾病负担。因此，如何在疾病早期对PD进行筛查识别，并在疾病进展期精准诊断PD成为PD临床诊疗的核心与挑战。

语音的产生依赖于包括呼吸韵律、声带振动、调音共鸣在内的各种运动的协调运作[1]；其中任何一种运动的障碍或不协调运作都会导致语音障碍的产生。作为一种全身的运动障碍性疾病，PD除了显著的且受临床评估重视的肢体运动障碍以外，同样普遍存在因为运动功能下降而导致的语音障碍问题[2]。据报道，PD患者中语音障碍的患病率可达近90%[3-4]，严重影响了患者的日常交流能力。

长久以来，PD的语音障碍评估主要依赖于相关专业医师的主观定性评估，语音表现为发音响度减弱、声音沙哑、语音听感粗糙、音调变化缺失等特点[5]。而随着技术的发展，声学分析技术可为语音评估提供诸多客观的定量指标，也进而使得利用语音声学分析实现PD的早期识别与精准诊断成为可能。本文将列举PD语音障碍声学分析相关研究进展，引入目前PD语音障碍评估中常用的声学指标，介绍其在疾病精准诊断、早期筛查及鉴别诊断的价值，以期提高对PD语音声学分析及其潜在诊断价值的认识。

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1　PD语音障碍常用的声学指标

声学分析技术为PD语音障碍的定量化提供了诸多特征指标。其中许多指标被证实与健康人群相比, PD患者存在不同程度的离群值现象。在PD语音评估中, 最常用的声学特征参数包括:

1.1　基频值（fundamental frequency, F_0）及基频变化幅度（fundamental frequency variation, vF_0）

F_0是语音信号的重要参数, 其提示了声门相邻两次开闭之间的时间间隔或开闭的频率。多项研究显示, PD患者由于咽喉肌及呼吸肌等相关肌肉强直[6], 常导致F_0升高[7-12], 听感上表现为患者的语音音调升高; 同时伴随vF_0升高[6, 11, 13-15], 听感上表现为患者稳态发音能力的下降。但值得注意的是, F_0的差异性可能受性别影响。HOLMES等[7]按性别将样本进行分层以后, 发现F_0只在男性PD患者相较于同性别健康对照有所升高, 女性PD患者F_0反而有所下降; SKODDA等[13]也观察到F_0仅在男性患者组中与健康对照差异有统计学意义。造成这样结论的原因之一, 可能是因为F_0近似反映声带振动快慢变化, 而男性和女性本身在声带长度、厚度以及振动频率上存在一定的生理差异。一般而言, 女性的F_0比男性要高。

1.2　频率微扰（frequency perturbation, Jitter）

频率微扰是描述发声相邻周期之间声波的基频变化的声学指标。PD患者由于声襞运动控制能力的下降及咽喉肌不规律收缩[16], 导致周期间的频率变化值增大, 即Jitter值升高[7, 10-12, 15, 17-19], 主观听感上表现为声音具有粗糙感。但另有研究发现Jitter值变化差异无统计学意义[6, 20]。

1.3　振幅微扰（amplitude perturbation, Shimmer）

振幅微扰与Jitter相似, 是描述发声相邻周期之间声波幅度变化的语音指标, PD患者由于声带振动的稳定性的下降, 同样会出现Shimmer的升高[8, 10-11, 15, 19-22], 主观听感上表现为声音嘶哑感。同Jitter一样, 也有文献报道Shimmer在PD患者与健康人群之间差异无统计学意义[6-7, 17-18, 20]。

1.4　谐噪比（harmonic-to-noise ratio, HNR）

HNR是语音信号中谐波与噪声的比值, 是反映声门闭合情况的重要指标。其中, 噪声来自于发声过程中声门不完全关闭产生的声音信号。PD患者由于声门控制能力下降, 进而气流紊乱形成噪音, 从而导致了HNR下降[11, 15]或噪谐比（noise-to-harmonic ratio, NHR）上升[10, 18-19]。但HOLMES等[7]研究发现NHR在PD患者与健康人群之间的差异不具有统计学意义。SILVA等[17]研究则发现PD患者存在NHR下降的特点。

此外, 其他生理或者声学指标诸如口腔轮替运动速率（diadochokinetic rate, DDK）[15, 23]、元音空间区域（vowel space area）[15, 18, 24]、发声起始时间（voice onset time, VOT）[15, 25]等众多指标都有相关文献报道。同时, 除去上述传统声学特征参数, 声学分析中的非线性参数也逐渐获得了相关重视, 包括循环周期密度熵（recurrence period density entropy）、去趋势波动分析（detrended fluctuation analysis, DFA）等[26-30], 其中DFA在PD检测中价值日益增高。DFA是研究语音信号中由于发声时气流通过声带等原因产生的随机噪声自相似程度的重要指标之一[31], SAKAR等[29]通过与统一帕金森病评定量表（Unified Parkinson's Disease Rating Scale, UPDRS）评分互信息（mutual information）分析发现DFA与UPDRS最为相关, 提示DFA可能是PD诊断乃至病情评估的重要标志物之一。

2　PD语音声学分析的诊断价值

承前所述, PD的语音障碍通过声学分析技术得以实现定量化的评估, 由此形成的诸多声学分析无疑为PD的精准诊断、早期筛查乃至鉴别诊断提供了全新而又可靠的维度。

2.1　结合机器学习算法的语音声学分析对于PD精准诊断的价值

介于PD患者与健康人群之间在诸多声学指标上存在差异, 声学分析无疑可以辅助PD的临床诊断。然而, 语音评估中可用的声学指标众多, 且在许多指标上PD患者与正常人群之间的区分度并未泾渭分明, 这成为了利用语音声学指标准确诊断PD的一大障碍。为了克服这一问题, 随着技术的发展, 基于机器学习算法的PD声学评估成为了一种必然选择——机器学习算法使得声学分析获得的数据不再停留于可以证实PD语音障碍的存在, 更可以将多种指标结合形成诊断系统, 将其运用于PD的判别之中, 也因此成为了研究的热点[26-27, 29, 32-40]。

举例而言, 仅仅通过一段10 s长度的/a:/语音数据, 利用提取到的声学指标, SAJAL等[35]使用K-近邻（k-nearest neighbors, kNN）分类算法实现了PD诊断98.3%的准确率; SINGH等[36]使用支持向量机（support vector machine, SVM）算法实现了PD诊断99.0%的准确率。甚至, ARORA等[38]使用普通语音通话级的录音质量, 在大规模真实世界队列中结合机器学习算法诊断PD即实现64.90%的敏感度及67.96%的特异度。因此, 声学分析产生的诸多特征参数为PD诊断提供了新的维度, 而结合机器学习算法的声学分析如虎添翼, 对于PD诊断有着巨大的应用价值与前景。

2.2 语音声学分析对于PD早期筛查的价值

PD的早期诊断及大规模人群筛查一直是临床亟待解决的重要问题之一。而已有诸多文献都报道了PD早期即可存在一定的语音障碍[41-45],且可能是最早出现的运动累犯表现,推测在临床诊断确立前9.8年即出现[46]。甚至,在PD的前驱疾病——快速眼动睡眠行为障碍(REM sleep behavior disorder, RBD)中即可显现[23, 43, 46-47]。这一早期出现的行为特性也与Braak分期[48],即PD周围自主神经系统及迷走神经、舌咽神经最早受累的特点相符。声学分析技术因其即使细小变化也可以精准捕捉的高灵敏性特点;加之其快速、无创、可远程开展等众多优点,有望成为PD早期筛查乃至早期诊断的重要手段之一。

鉴于PD前驱期,即疾病开始进展而核心症状还未显现或显著的时段难以被临床研究纳入考量,因此少有基于PD前驱期患者的相关研究。而介于RBD患者远期出现以PD为主的神经退行性疾病概率极高[49-50],因此RBD患者人群将会是用于检验声学分析是否能用于PD早期筛查的良好对象。HLAVNIČKA等[47]已发现RBD患者在轻塞音时长(duration of unvoiced stops, DUS)、朗读/独白时停顿长度(duration of pause intervals in monologue, DPI)等指标上与健康人群之间有明显区别;RUSZ等[23, 43]同样也发现RBD患者中即存在构音障碍,F_0变异度、言语时率(rate of speech timing, RST)、共振频率衰减(resonant frequency attenuation, RFA)、口腔轮替运动规律性(diadochokinetic regularity, DDK regularity)与健康人群间差异有统计学意义;结合多个语音指标,可实现区分RBD患者与健康人群96%的敏感度与79%特异度。介于此,PD语音障碍的声学分析有望实现PD的早期识别诊断,但目前相关研究较少,有待进一步更多的研究确证其可靠性。

2.3 语音声学分析对于帕金森综合征鉴别诊断的价值

在临床诊断中,进行性核上性麻痹(progressive supranuclear palsy, PSP)、多系统萎缩(multiple system atrophy, MSA)等非典型帕金森综合征疾病在临床上需要与PD相鉴别,但其临床表型与PD具有较高的相似性,难以明确诊断。然而,PSP[51-52]及MSA[51, 53-58]也存在不同程度的语音障碍,甚至在疾病确诊前即可出现[55]。

更重要的是,不同病种都具有各自特有的语音发声表现,有望作为标志物用于鉴别诊断中[59-60]。例如,RUSZ等发现PD患者相较于PSP患者及MSA患者节律加速现象更显著[57],且通过结合HNR、语速、语音震颤指数及流利度评估指标4个维度的声学信息可实现PSP患者与MSA患者间的鉴别诊断(准确度75%)[61]。HUH等[58]发现在MSA-P与PD的男性患者中,MSA-P型患者与PD患者相比在阅读短文最后一句时,在语速、词间停顿时间等指标上的差异有统计学意义。TYKALOVA等[25]研究VOT时发现,PSP患者与MSA患者在发清爆破音时相较于PD患者差异有统计学意义,但PSP患者与MSA患者之间差异无统计学意义;而在发浊爆破音时PSP患者与MSA患者之间差异有统计学意义。综上,将声学分析运用于帕金森综合征的鉴别诊断具有十分重要的临床意义和应用前景,值得进一步深入研究。

3 小结与展望

PD患者语音声学指标与健康人群相比具有明显的差异性,与其他非典型帕金森综合征疾病也具有一定的区别。因此,语音声学分析为PD的诊断提供了全新的维度,也有望实现PD的精准诊断、早期筛查乃至鉴别诊断。此外,亦有部分研究也提示语音声学分析可能成为疾病进展的标志物[62-64]。SKODDA等[62]发现随着病程进展,Shimmer、NHR等指标与基线相比存在显著的差异性。RUSZ等[64]基于HNR、VOT等8个声学指标形成复合语音障碍指数(composite speech impairment index, CSII),数值越高代表语音障碍更为严重;对14位初发未治且病程中未使用药物的PD患者随访12个月后发现CSII值较基线显著升高,提示语音障碍加重。语音声学分析在疾病进展判别的应用价值有待进一步探索。加之语音采集独有的快速、无创、可远程开展等优点,语音声学分析势必在PD疾病诊疗中具有良好的应用前景。

但与此同时,我们也注意到虽然众多研究都不同程度提示了声学指标对于PD的诊断价值,但不同研究的结论缺乏一致性。其原因在于语音作为一种深度复合表型受到诸多因素影响[65],包括性别[7, 13, 58]、语音测量范式[25, 47, 51, 58, 66-68]、患者母语特点[69-70]、录音质量[38]等。这些因素可能造成了同一种疾病在不同研究中结论的异质性。举例而言,针对同一个样本人群,YANG等[66]发现采取不同的范式,同一语音指标可以得到不同的结果甚至趋势;HLAVNIČKA等[47]则发现让患者进行文章阅读和独白两种范式时,同一语音指标在范式间的差异具有统计学意义。据此,规范化各研究中心语音录取流程及分析方法,同时结合各地区语言特点进行语音评估是目前急需解决的问题。2020年12月,*Movement Disorders*杂志刊登了RUSZ等所著的关于开展运动障碍疾病语音评估的指南意见[15],其提出了建议的录音环境、录音范式、分析指标等内容,这为未来各研究中心进行同质化的语音声学分析提供了坚实基础。与此同时,介于语音的复合表型特

性, 一方面声学指标因此具有高敏感性, 任何细小的病变也可能导致声学指标产生变异从而被捕捉实现; 但也因此其特异性可能较弱, 咽喉疾病、呼吸系统疾病等众多疾病都可导致相同的声学指标变化。目前, 少有相关研究同时将多个跨领域病种纳入研究队列中, 声学分析的特异性价值有待进一步回答。此外值得注意的是, 目前大多数相关研究的研究对象都是基于以英语为母语的人群队列, 可能存在因患者母语而导致的巨大选择性偏倚。英语是一种非声调语言而汉语是一种有声调语言, 具有区别意义的声调变化本身也会使得我们关注的声学特征产生较大的变化。因此, 上述诊断价值的评价、选取的指标能否适用于汉语群体, 甚至是全人群需要保持谨慎的态度。

即使目前的相关研究还存在一些不足, 但可确定的是, 声学分析得出的语音指标已经成为了PD诊断的重要标志物之一, 并具有广阔的应用价值与前景, 有待进一步研究确证以期辅助临床医师的诊断工作。

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利益冲突　所有作者均声明不存在利益冲突

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