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Hans汉斯

基于脑分割技术对性别与年龄在脑结构体积中影响的研究进展

申博兴[1]，李延静[2*]

[1]延安大学附属医院，陕西 延安
[2]延安大学附属医院放射科，陕西 延安
Email: 315841210@qq.com, *lixiang_068@163.com

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摘　要

随着社会发展，现代中国的老年化问题日益加重，正常人老年化过程中常导致神经退行性改变，引起灰质及白质的体积不同改变。现有研究证明脑萎缩与多种疾病相关，有的疾病甚至有直接相关，对我国的老年化群体及家庭造成很大负担。明确健康人大脑灰质、白质结构随年龄变化特点，从而进一步探索大脑退化的规律成为近些年国内外神经影像学科的重点研究问题。当进行脑体积神经影像分析时，年龄、性别和头部大小(颅内容积)是最常见的变量，所以探究这些因素的影响成为当前研究的热点。本综述多选取pubmed近五年脑容积改变相关外文文献，分析不同性别健康人脑灰、白质体积随年龄的变化特点，从而进一步探索脑老化变化规律。

关键词

脑分割，体积，性别差异，增龄性脑改变

Research Progress on the Influence of Gender and Age in Brain Structure Volume Based on Brain Segmentation Technology

Boxing Shen[1], Yanjing Li[2*]

[1]Yan'an University Affiliated Hospital, Yan'an Shaanxi
[2]Department of Radiology, Yan'an University Affiliated Hospital, Yan'an Shaanxi
Email: 315841210@qq.com, *lixiang_068@163.com

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*通讯作者。

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Abstract

With the development of society, the problem of aging in modern China is becoming more and more serious. In the process of aging, normal people often lead to neurodegenerative changes, resulting in different volumes of gray matter and white matter. Existing studies have proved that brain atrophy is related to a variety of diseases, and some diseases are even directly related, which causes a great burden to the aging groups and families in our country. In recent years, it has become a key research issue in neuroimaging field at home and abroad to clarify the characteristics of changes of gray matter and white matter structure in healthy people's brain with age, so as to further explore the law of brain degeneration. When brain volume neuroimaging analysis is carried out, age, sex and head size (intracranial volume) are the most common variables, so exploring the influence of these factors has become the focus of the current research. This review mainly selects the foreign literature related to the changes of brain volume in the past five years of pubmed, and analyzes the characteristics of brain gray and white matter volume changes with age in healthy people of different genders, so as to further explore the changes of brain aging.

Keywords

Brain Segmentation, Size, Gender Differences, Aging Brain Changes

1. 颅脑形态学研究

脑科学一直以来是科学研究的所关注的方向。人脑发育变化遵循“结构－功能”改变模式，脑结构的变化常常与人们的认知及精神状况紧密相关，而 MRI 技术的快速发展使人活体脑的研究成为可能，新的扫描成像技术为临床进行精确性的形态学研究供了有效的手段。目前国内外探讨关于活体脑容量改变主要采用 MRI 扫描，采用具有较高全脑分辨力、高清晰度及较好的灰白质对比优势的 3D-T1 磁化准备快速梯度回波序列(3D T1 MP RAGE)，有利于分割与测量。而形态学测量技术当前分为以下几种：感兴趣分析法(ROI)、基于体素的形态学测量(VBM) [1] [2]、基于对象(脑回/脑区)的形态学测量(OBM) [3] [4]。感兴趣分析法用于早期脑分割领域研究，依赖操作者的知识与经验，可重复性与一致性较低；基于体素的形态学测量存在空间标准化及硬性匹配造成的误差较大，且时效性难以满足在临床工作的问题；OBM 则通过对“组织”的自动识别与提取分割，随着人工智能在医疗工作中的广泛开发利用，时效性及稳定性得到保障，在以后的临床及科研方面具有较好的前景。当前研究重心在基于形态学研究健康成人脑在年龄及性别改变的同质性，进一步明确其退化规律。

2. 脑结构的变化

2.1. 颅脑的结构不对称性

随着现代医工学科发展，脑体积测量研究深入研究，现阶段发现大脑半球及其结构体积的不对称性在健康人脑中普遍存在，而近来报道却尚无一致性。Lehtola SJ [5]认为在婴幼儿阶段右颞叶，左顶叶和枕

叶的体积更大，而不对称程度不随年龄变化；Király A [4]认为在成人阶段仅男性组大脑偏侧化，右侧尾状体和左侧丘脑的体积更大，此外 Kijonka M [6]认为这种结果这是因为在衰老过程中左尾状核和右丘脑萎缩加速所致。而 Wang Y [3]提出皮层下灰质结构存在不对称性，不对称性系数 = (左体积 − 右容积)/平均值(左容积，右容积) × 100%。这个不对称指数反映了偏侧程度(>0 为左偏，反之则右侧)，并且认为尾状核及海马不对称系数与年龄呈线性关系，左侧尾状核随年龄增长持续减少直至接近对侧尾状体，呈左偏趋势，尤其在男性；女性海马随年龄逐渐呈右偏趋势，男性海马则呈左偏趋势；而苍白球不对称系数与年龄呈正二次相关，但始终呈左偏，而在 45~50 岁双侧苍白球最接近，性别差异较小，这可能与右侧苍白球下降速率快有关。现阶段认为脑结构偏侧化与可能与优势肢体或优势感有关，有研究认为大脑的偏侧化是所有脊椎动物的大脑组织的基本特征[7]；例如优势肢体与海马体积分布有关[8]，左利手呈现左侧海马优势分布，反之则右侧。但此外尚无一致性研究文献报道，这可能与之前研究样本量、研究方法及图像处理的差异性有关，此项研究在近后人工智能领域应用下可能会有所发现。然而明确颅脑偏侧化可能有助于认识与鉴别相关疾病，如慢性精神分裂症与皮层下体积偏侧化改变有关[9]，而涉及苍白球体积左偏不对称的增加，并且认为这可能是精神病易感性的基础；而左侧大脑皮质厚度异常与癫痫病患者有关[2]，女性多见于颞部，而男性的额叶区域受影响更大。

2.2. 全脑体积变化

全脑在发育－衰老过程中，相关研究认为全脑体积(TBV)与年龄呈非线性相关，呈倒“U”型增长模式，在青春期(10~12)岁之间 TBV 达到高峰，之后随着年龄的增长，全脑体积下降，尤其女性 TBV 与年龄呈显著负二次拟合相关[10]。虽然有发现在原始体积中男性 TCV 明显大于女性[6] [11]，但而这种差异皆与颅内体积(ICV)有关，在除去 ICV 干扰后，两种性别的全脑容量无显著性差异[4]。总脑容量(TBV)为灰质和白质体积的总和。颅内容积(ICV)为 TBV 和脑脊液(CSF)容积之和。成人之后颅内容积几乎不会随年龄改变[12]，但全脑容积随年龄的增加而逐步减少，脑脊液体积则随之增加，灰质体积(GM)与年龄呈负相关[13]，脑脊液体积与年龄呈正相关趋势。此外由于全脑的稳定性，通过颅内容积(ICV)对形态计量学分析进行归一化以校正头部大小数据，并被认为是减少对脑容积的错误统计解释的基础，并为患者之间的比较提供了依据[14]。Rodrigues M [11]认为 60 岁后 TCV 每十年减少 2.4%，灰质和白质均随年龄增长而减少，这与以前的研究报道的比率相当，此研究对基础脑退行性体积改变提供了对照。

2.3. 白质体积变化

而总白质体积随年龄呈倒“U”型二次分布，在 40 岁之前逐渐增加，在 50 岁左右达到峰值，而在 60 岁之后迅速下降[1]，至今未发现报道白质体积上年龄和性别之间的相互作用[10]，但是 Pfefferbaum A 等人[15]发现衰老时白质体积男性比女性下降的幅度更大，而其他研究报告了白质老化的性别差异性，相同的 37 对大脑大小相配对情况下，女性的胼胝体体积明显增大[16]。令人值得注意的是，性别及年龄相关的 WM 完整性丧失及体积的差异是脑白质老化的区域，老年人具有雌激素受体 1 等位基因的女性表现出明显较小的 WM 病变，提示雌激素对年龄相关的 WM 损伤具有保护作用[17]，这对解释颅脑体积在性别差异中提供了参考价值。

对于白质与年龄的二次拟合趋势，Farokhian [13]等人解释可能是由于白质在正常衰老过程中不断成熟所致，而这种变化差异性可能与白质发育及老化过程中各部分的不同步所致[1]，在衰老过程中双侧额叶和双侧颞叶是最早出现的脑白质体积下降的脑区，而枕叶是最后一个显示白质变化的大脑区域，在发育过程中额叶髓鞘形成出现最迟，而枕叶则最早出现。白质老化符合“先进后出”的假说，即先成熟的脑区最后老化，在额叶，髓鞘较薄，修复机制效率较低，少突胶质细胞易受到代谢损伤，尤其是铁介导

的损伤。因此双侧额叶白质是在老化过程中受损程度最大的脑区，即与年龄的相关性最强，并且易引起髓磷脂及铁丢失[18]。而基于动物病理的研究发现，与年龄相关的脑白质结构改变主要是脑实质细胞减少以及伴随纤维的损失，而与轴突损失关系不大，而神经纤维的减少则常常导致认知功能减退。

有研究报告白质改变与精神性疾病的关系紧密相关。例如在 DTI 研究中，发现到精神分裂症患者在由于年龄相关的白质和纤维束 FA 值显著减低，并发现相关纤维有加速老化及异常发育的神经病理模式[19]。而在抑郁病研究中发现抑郁症与白质显示额叶边缘回路的白质改变有关，涉及丘脑后辐射等多个脑区域，同时进一步利用抑郁症的实际分类定义以及临床表型变异性解释相应白质完整性改变[20]。老年性白质改变与精神疾病易感性的关系在以后的研究中值得探索，建立健康脑白质体积衰老变化则有助于理解这类疾病变化机制。

2.4. 灰质体积变化

众多研究发现男性绝对体积较大，女性相对灰质体积较大在儿童[21]和成人[22]，而在扫描时调整年龄和 TBV 时，并未发现显著的性别差异[10]。而 Lehtola 等人[5]并不认可性别差异性的存在。

在当前的研究中，脑灰质在发育至儿童阶段成熟。体积达到最大化，之后则随年龄减低，随着年龄增长，灰质总体积呈线性下降[22]，各皮层区域灰质体积呈显著负相关，而老化时序性同样支持“先进后出”的假说，最易受损的是双侧额叶，而枕叶灰质体积很少见体积变化；有研究证明与年轻人相比，老年人额叶、岛叶和扣带回皮质的灰质体积普遍减少[13]。早期灰质体积减低可能与白质微结构及皮质的连接区域有关[23]，可能反映了树突结构、白质结构和突触的许多脑组织成熟过程，这些区域随年龄增长继发引起灰质体积相对减少，这种相对萎缩通常并非涉及到神经细胞本身。而老龄性灰质减少被认为是神经元萎缩，现阶段研究共识可能是细胞缩小和树突结构减少有关而很少涉及神经元数量的减少[24]。此外在衰老速率方面，在进行全脑体积的调整后，男性灰质体积与年龄负相关更为明显，而女性灰质体积的负年龄依赖性较弱[6]。

2.5. 皮层下灰质体积变化

皮层下灰质结构包括双侧丘脑、豆状核、海马、杏仁体及尾状核。既往研究中认为丘脑及海马体积变化符合负二次曲线模型[4] [10] [25]，在 20 岁~80 岁之间，在 20~30 之前与年龄相关的体积趋势升高，在 20~30 岁体积变化区域平稳，之后下降；而在 60 岁以后发现两者体积下降速率男性中减少得更快[4] [26]，而这可能与性激素浓度变化关系紧密有关；有研究报告丘脑体积的减少与睡眠中的癫痫持续状态密切相关[27]。有关文献报道了海马局部体积的性别相关差异，观察到与性别有关海马体积差异，这些差异是右侧海马，左右海马头部[28]。而众多文献对于海马研究主要集中在认知及记忆功能，而在整个衰老过程中与海马亚区体积差异会影响情节记忆能力[29]，主要参与亚区主要有在海马 CA2/3 区[30] [31]，Jiang L [30]发现一定的教育程度在男性中有助于改善该体积损失，从而延缓衰老，改善认知记忆；此外海马体积异常损失还表现在一些精神性疾病中，如海马萎缩在 AD 中的最重要指标及海马硬化痫性发作[32]的病理机制中均有重要作用。

豆状核、杏仁核及尾状核在既往研究中发现其体积随年龄而减少或轻微变化[4] [6] [10] [33]，而在尚未发现显著年龄与性别的交互作用。但是发现这些皮层下灰质结构均与某些临床病理变化有关，例如苍白球的受损已在缺血，酒精[34]和鸦片滥用中报道过，继而引起各种认知和运动问题。而在病理情况下苍白球的损伤则引起基底神经节通路功能障碍如帕金森疾病及亨廷顿氏病[35] [36]等；杏仁核通常被认为与情感评估有关，杏仁核在抑郁症的病因中起着关键作用，有研究发现抑郁症患者疾病表现为灰质体积明显减少杏仁核[37]，并且抑郁症严重程度始终与杏仁核体积呈负相关，导致抑郁症状恶化[38]，此外恐惧

及威胁情绪亦会引起其体积减少[39] [40]。尾状核在行为执行过程中有着重要意义，包括基于对行动结果的评估及通过调节奖励注意关注来参与决策，并且调节注意力来调节场景转化，例如尾状核的不对称性可能是注意缺陷多动障碍患者的标志[41]。

3. 脑结构性别差异假说

近年来越来越多的报道证明了女性减缓大脑组织结构衰老引起的萎缩，而这种有益性是不同步的及不均匀的。虽然男性和女性脑体积差异变化的机制尚未被阐明，但激素水平的变化以及由此导致的大脑对激素影响的敏感性是最肯定的。神经类固醇甾体在大脑中生物合成并在脑发育及衰老过程中发挥着重要作用[42]。有研究证明神经活性类固醇在扣带回、顶叶和枕联合皮质的多个区域，异丙孕酮和孕烯醇酮水平与灰质厚度呈正相关[24]。一项纵向研究表明性激素预测了青春期男女右侧杏仁核的生长[43] (睾酮与杏仁核体积有关，男孩右杏仁核体积减小，女孩增大)。

并且有研究证明孕酮及雌激素在发育过程中结合脑内雌激素与孕激素受体，促进髓鞘形成、棘突形成、突触形成、神经元存活和树突生长[44]，发挥着神经保护和抗炎作用[45] [46]；绝经前后和绝经后长期的雌激素水平低下可能会增加老年妇女对脑退化和年龄相关疾病的脆弱性，加速衰老的表现。

此外有研究持有不同论点，Duong [47]等人认为在类固醇激素保护神经元存在“机会窗”，只有在健康神经细胞内可以发挥抗氧化应激损伤的作用。

另一种观点认为脑性别分化及脑结构的差异性可能受基因调控[48]，其中一些研究提出来一些基于“女性保护”机制的假设，包括性染色体效应[49]，性染色体可能在塑造大脑结构和性别差异方面有关，导致男性在神经解剖学表现出更大的变异性。

4. 脑分割前景与未来

综上所述，进一步理解脑萎缩发展规律，可以早期识别或诊疗相关脑科领域疾病，而在正常人脑结构体积差异在年龄与性别方面影响因素较为突出，此外在其他方面相关文献在睡眠时间限制、脂肪含量过高及社交能力差异等方面均存在报道，而这些外部因素可能会干扰正常人颅脑变化差异性研究。然而在脑容量越来越多地被用作临床指标情况下，所报告的脑结构形态测量结果依然存在不一致，这可能与纳入样本特征(受试者的年龄、人数和种族)、扫描模式及图像分析方法的差异有关，这些都给神经科学中大脑结构及功能研究带来了重大挑战。因此，有必要对大脑结构体积的正常值进行评估，并且提供客观且可靠的参考值，以减少由于患者的性别或年龄造成的偏差而导致的错误决策，为患者提供更为优质医疗资源，有助于脑科学相关领域更好地发展。

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