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医学影像物理

脑部弥散张量成像数据处理技术在疾病诊断研究中的应用进展

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【摘 要】主要介绍弥散张量成像(Diffusion Tensor Image, DTI)技术的发展,介绍脑部DTI数据处理常用的方法应用于疾病诊断的发展概况。本文总结DTI数据处理最常用的3种方法,包括基于体素的分析、基于纤维束的空间统计分析方法和白质纤维追踪方法,其中列出了使用各种方法应用于疾病研究所取得的成果,对研究结果进行了分析并对各种分析方法的优缺点进行总结。最后对DTI的发展方向提出展望,DTI在科研和临床应用方面都发挥着越来越重要的作用,尤其是科研方面已取得很多重要成果。在临床方面,DTI可用于多种疾病的诊断和治疗,且在某些疾病的诊断中发挥着越来越重要的作用。

【关键词】脑;弥散张量成像;基于体素的分析;基于纤维束的空间统计分析方法;纤维追踪
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Review of disease diagnosis research based on brain diffusion tensor imaging data processing technique

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Abstract: The development of the diffusion tensor imaging (DTI) technology is introduced in the paper, including the development of the most commonly used method of the brain DTI data processing and application in disease diagnosis. Three most commonly used DTI data processing methods are summarized, including voxel-based analysis, tract-based spatial statistics, and white matter fiber tracking method, in which the achievements of various methods applied to disease research are listed, and the research results are analyzed, and the advantages and disadvantages of various analysis methods are summarized. Finally, the perspectives on the future research direction of DTI are offered. DTI is playing an increasingly important role in scientific research and clinical application. Especially, many important achievements are made in scientific research. In clinic, DTI can be used in the diagnosis and treatment of various diseases, and plays a more and more important role in some disease diagnosis.

Key words: brain; diffusion tensor imaging; voxel-based analysis; tract-based spatial statistics; fiber tracking

前 言

随着医学影像学的发展,弥散张量成像(Diffusion Tensor Imaging, DTI)成为一种广泛被人们认可和应用的医学手段。DTI在脑网络连接方面提供的独特视角,使其在某些特殊疾病的诊断和治疗过程中,发挥着不可替代的作用。

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1 DTI成像技术的发展

1.1 DTI原理简介

在完全均匀的介质中,水分子是各向同性弥散的;而在不完全均匀的介质中,水分子是各向异性弥散的。因此,在大脑的不同组织中,水分子的弥散情况是不一样的。在脑脊液和灰质中,水分子的弥散近似各向同性;而在白质中,水分子的弥散是各向异性的。目前普遍认为,水分子的最大弥散方向与白质纤维的方向是一致的,这些信息包含在弥散张量中[1-3]。根据这一原理,我们可以利用水分子的弥散状况来推测白质纤维的走向以及连接情况,从而为疾病的诊断和治疗提供依据。

1.2 DTI技术的改进

DTI在数据获取时，其数据质量受b值（表示弥散加权信号衰减的速度）[4]、磁场强度、头动、采集时间等多种因素的影响。因此需要对DTI数据进行严格的预处理，以得到适用的图像，在此过程中，伪影校正和配准尤为关键。近年来，许多研究人员对伪影处理和配准方法的改进做了很多研究，期望DTI预处理过程更为严谨，结果更为精准[5-6]。

2 DTI数据处理常用的方法

DTI在探测白质完整性、描绘中枢系统神经结构的方向性和联系性方面取得重要成果。如今，DTI被广泛用来研究正常生理学和病理生理学变化过程中白质的联系，包括大脑的发育和老化、神经病学和精神病学的多种病症、大脑损伤和肿瘤、认知功能等[4]。DTI的统计量与结构改变有关，如各向异性指数（Fractional Anisotropy, FA）、平均弥散率（Mean Diffusivity, MD）、轴向弥散率（Radial Diffusivity, RD）、径向弥散率（Axial Diffusivity, AD），可以表明特定髓鞘的形成水平和轴突损伤的情况[5]。

常用的DTI分析方法包括基于体素的分析（Voxel-based Analysis, VBA）、基于纤维束的空间统计分析方法（Tract-based Spatial Statistics, TBSS）和白质纤维追踪方法。

2.1 VBA的大脑结构异常分析方法

VBA过程是自动的，要求最少介入，不受用户个人影响，是在全脑水平上进行的研究，结果比较快速、客观。VBA分析方法对配准错误有很高的敏感性并且在配准失误的地方会产生假阳性，但是随着配准方法的改进，VBA仍然广泛应用于核磁图像的研究。

2.2 TBSS的大脑结构异常分析方法

由于VBA分析过程无法克服的缺点，现在部分研究人员更倾向于使用TBSS方法。TBSS主要由于骨架投影步骤而减少了局部错误配准带来的影响，并且不必空间平滑，统计能力也有所提高。它的一般实现过程是：（1）通过非线性配准将所有被试的FA图对齐到预先确定的目标FA图；（2）通过仿射配准将所有对齐的FA图像转化到（1×1×1）mm^3的MNI152空间；（3）从MNI152空间选择所有被试的数据集创造平均FA图像及其骨架；（4）将个体被试的FA图投射到骨架上；（5）对共同的骨架上的每个点于不同被试间进行体素层面的统计。

2.3 基于白质纤维束追踪的大脑结构异常分析方法

VBA与TBSS方法都是基于体素层面的分析，其重点是对各项弥散指标的计算、比较和分析，反映的是白质纤维完整性的情况，包括轴突损伤和退化、髓鞘的损伤和跨纤维弥散的自由度增加等。但是，这两种方法都没有直观准确地反应白质纤维束在大脑全部区域或部分区域的走向和连接状况，所以很多研究者会采用白质纤维追踪的方法来直观探究白质纤维束的走向。纤维追踪过程分为3步，分别是选取种子点、传播和停止。被试的不同、种子点选择的不同以及追踪工具的不同，导致追踪结果不一。种子点的选取一般有两种方法：一是在感兴趣区域的每个体素内放置一个或多个种子；二是全脑自动选取种子点的方法。传播的过程也有两种方式：确定性和概率性。终止时最常用的标准是：最小FA阈值（通常成人大脑内0.1~0.3，未成年人0.1）和转角阈值（取决于路径，通常40°~70°）[5]。

大脑某些特定区域内，在一个体素中可能包含两个或更多不同方向的纤维束（交叉、分叉或交缠的纤维），这导致了对纤维方向和路径的错误评估以及追踪的突然中止。这一直是纤维追踪的一大难题，需要利用较为复杂的方法或某些特定软件来解决。例如，基于限制球形反卷积的概率纤维追踪技术允许一个体素内有不同的纤维方向，其在包含平行或切向的纤维交叉的白质区域比传统纤维追踪的鲁棒性要好[6]。

3 DTI数据处理在疾病研究中的应用

近期一些基于VBA的DTI图像研究成果如表1所示。表1涉及到的几种疾病，患者与健康被试相比，大部分患者的FA降低、MD升高，这表明患者大脑内的白质纤维束髓鞘完整性受到了损伤。

尽管通过严谨的过程后，VBA分析方法可以得到有效的结果，但是仍有部分学者对该方法持怀疑态度，认为到底是由于体素密度改变还是局部配准错误导致的，很难区分。其中一个问题是：怎样保证每个被试配准到共同空间时是完全成功的，尤其考虑到其拓扑学变量和每一个结构的准确配准？另外，平滑程度严重影响最后的统计结果（平滑程度过大会引起较大的部分容积效应），但现在并没有一个确切的标准来衡量平滑程度是否适中[19]。这些问题仍需进一步的研究来解决。

近期一些基于TBSS的DTI图像研究成果如表2所示。

表2涉及到的几种疾病，患者与健康被试相比，大部分FA有所下降且MD、RD、AD等有所上升，这与VBA方法分析的结果相近。在DTI指标的定量计

表1 基于VBA的DTI图像大脑结构异常研究

Tab.1 Abnormal brain structure research on DTI based on VBA

Reference	Subject	Result
Shu (2009)[7]	Early blind (17); HC (17)	Compared with HC, regions with FA decreased, and MD increased in the early blind (blindness onset was within 1 year for all blind subjects): bilateral lingual gyri, and temporal-occipital regions, including middle occipital gyrus, cuneus, and sub-gyral of temporal lobe. No region with higher FA in the early blind was found.
Li (2010)[8]	ADHD (24); HC (20)	Compared with HC, regions with FA increased in ADHD was right frontal lobe.
Konrad (2010)[9]	ADHD (37); HC (34)	For adult patients with ADHD, reduced FA as well as higher MD present bilaterally in orbitomedial prefrontal WM, and in right anterior cingulate bundle, while elevated FA was present bilaterally in temporal WM structures.
Davenport (2010)[10]	Schizophrenia (15); ADHD (14); HC (26)	Compared with ADHD patients and HC, schizophrenia patients had uniquely low FA in bilateral cerebral peduncles, anterior and posterior corpus callosum, right anterior corona radiata, and right SLF. ADHD patients had uniquely high FA in left inferior and right superior frontal regions. Both clinical groups had lower FA than HC in left posterior fornix.
Peterson (2011)[11]	ADHD (16); HC (16)	Using voxel-wise analysis, fractional anisotropy was found to be significantly increased in the ADHD group in right superior frontal gyrus, posterior thalamic radiation, left dorsal posterior cingulate gyrus, lingual gyrus, and parahippocampal gyrus. No regions showed significantly decreased FA in ADHD.
Qiu (2011)[12]	ADHD (43); HC (43)	Compared with HC, ADHD patients had significantly decreased FA in forceps minor, internal capsule, corona radiata, splenium of corpus callosum, and bilateral basal ganglia.
Li (2013)[13]	Monocular amblyopic children (20); HC (20)	Compared with HC, monocular amblyopic group showed reduced GMV in left inferior occipital gyrus, bilateral parahippocampal gyrus, and left supramarginal/postcentral gyrus, and increased GMV in lingual gyrus. Meanwhile, WMV of monocular amblyopic group reduced in left calcarine, bilateral inferior frontal, and right precuneus areas, while increased in right cuneus, right middle occipital, and left orbital frontal areas. Diminished FA values in optic radiation and increased FA in left middle occipital area and right precuneus were detected in amblyopic patients.
Emsell (2013)[14]	Bipolar I disorder (19); Unaffected first-degree relatives (21); HC (15)	Compared with HC and relatives, regions with reduced FA and increased MD were observed in cingulum, SLF, callosal splenium, and ILF of patients. In the tractography study, WM microstructural abnormalities in limbic, temporal and callosal pathways were detected in patients.
Nir (2013)[15]	Alzheimer's disease (23); MCI (88), including early-MCI (62), late-MCI (26); HC (44)	Compared with HC, Alzheimer's disease patients showed pervasive deficits in fiber integrity (lower FA). The higher mean RD, AD and MD values were found in Alzheimer's Disease patients, and the effects were larger and even diffuser than for FA. No significant difference was detected between early-MCI and late-MCI groups in any of the DTI measures. No significant difference in the anisotropy or diffusivity measures was found between HC and MCI as a whole, or HC and the early-MCI group. However, significant difference were found in the RD, AD and MD of left hippocampal part of cingulum between HC and late-MCI group.
Yang (2015)[16]	Patients with ischemic stroke during convalescence (54), dividing into apathy (31) and non-apathy (23)	Significant FA reduction was detected in four clusters with peak voxels at callosum, left anterior corona radiata, splenium of the corpus callosum, and right inferior frontal gyrus.
Chaim (2014)[17]	ADHD (22); HC (19)	Compared with HC, ADHD patients showed reduced GMV in right angular gyrus, and increased GMV in right supplementary motor area and superior frontal gyrus, and higher FA in WM of bilateral superior frontal gyrus, right middle frontal left gyrus, left postcentral gyrus, bilateral cingulate gyrus, bilateral middle temporal gyrus, and right superior temporal gyrus. Compared with HC, some higher diffusive parameters (mean diffusivity and axial diffusivity) in ADHD patients were also found in fronto-striatal-parieto-occipital circuits, including right superior frontal gyrus, bilateral middle frontal gyrus, right precentral gyrus, left middle occipital gyrus and bilateral cingulate gyrus, as well as the left body and right splenium of the corpus callosum, right superior corona radiata, and right SLF and fronto-occipital fasciculi.

续表1（Continued Tab.1）

Reference	Subject	Result
Allen (2015)[18]	Adults with amblyopia (10); HC (10)	No significant difference was found in the diffusion properties in cortico-cortical pathways of patients with amblyopia who exhibited increased MD in thalamo-cortical visual pathways.

DTI: Diffusion tensor image; VBA: Voxel-based Analysis; HC: Healthy control; FA: Fractional anisotropy; MD: Mean diffusivity; ADHD: Attention-deficit/hyperactivity disorder; WM: White matter; SLF: Superior longitudinal fasciculus; GMV: Grey matter volum; WMV: White matter volume; ILF: Inferior longitudinal fasciculus; RD: Radial Diffusivity; AD: Axial Diffusivity; MCI: Mild cognitive impairment

表2 基于TBSS的DTI图像大脑结构异常研究

Tab.2 Abnormal brain structure research on DTI images based on TBSS

Reference	Subject	Result
Aliotta (2014)[20]	POMS (16); AOAMS (23); AODMS (22)	Compared with POMS, widespread cortical and deep WM area differences characterized by increased FA values were seen in AOAMS. Significantly increased FA values of posterior WM areas were also detected in AODMS.
Liu (2013)[21]	Schizophrenia (17); HC (17)	Schizophrenia patients showed significant FA reduction in left ILF and left IFOF, and no difference in MD, AD or RD as compared to HC.
Lee (2013)[22]	First-episode schizophrenia (17); HC (17)	Compared with HC, First-episode patients with schizophrenia showed lower FA values in the genu and body of corpus callosum, internal capsule, external capsule, fornix, superior or inferior fronto-occipital fasciculus, cingulum, and uncinate fasciculus. Increased MD and RD were shown in virtually all white matter regions. No significant difference in AD was observed between the two groups.
Liu (2014)[23]	Medicated-naïve chronic schizophrenia patients (17); HC (17)	Schizophrenia patients possessed lower FA values in left IFOF and left ILF, along with smaller GMV and cortical thinning in temporal lobe than HC.
Haney-Caron (2014)[24]	CD (17); HC (24)	CD adolescents had significantly lower FA and AD values in frontal lobe and temporal lobe regions, including frontal lobe anterior/superior corona radiata, ILF and fronto-occipital fasciculi passing through the temporal lobe.
Hanneke (2014)[25]	ADHD (170); Unaffected siblings (80); HC (107)	Individuals with ADHD showed decreased FA and decreased MD in several widespread, non-overlapping brain regions. In contrast, higher ADHD symptom count was consistently associated with increased FA and decreased MD in ADHD group. Unaffected siblings resembled individuals in the ADHD group with regard to decreased FA but had MD similar to that in HC.
Onnink (2015)[26]	Adult ADHD (107); HC (109)	In comparison to controls, participants with ADHD showed reduced FA in corpus callosum, bilateral corona radiata, and thalamic radiation. Higher MD and RD were found in overlapping and even more widespread areas in both hemispheres, also encompassing internal and external capsule, sagittal stratum, fornix, and superior lateral fasciculus.
Lawrence (2015)[27]	WD (35) including treatment-naïve patients (18) and patients already on decoppering therapy (17)	The entire cohort had significant improvement in all the four parameters (MD, FA, AD and RD) indicated by a decrease in MD, AD and RD values and increase in FA values. Comparison of whole-brain white matter DTI measures between pre- and post-treatment did not show any significant difference.
Li (2015)[28]	Amblyopic children (20); HC (20)	In contrast to the controls, significant decreases in FA values were found in right optic radiation , left ILF/IFOF and right SLF in the amblyopia.
Chen (2015)[29]	Alzheimer's disease (12); HC (12)	The FA of cingulum, hippocampus, corticospinal tract, and IFOF significantly reduced in Alzheimer's patients than that of HC. On the other hand, the FA of other encephalic regions had no discrepancy compared with that of HC.

TBSS: Tract-based spatial statistics; AOAMS: Age-matched adult-onset patients with multiple sclerosis; AODMS: Disease duration-matched adult-onset patients with multiple sclerosis; POMS: Pediatric-onset multiple sclerosis; IFOF: Inferior fronto-occipital fasciculus

算中，无论是VBA方法还是TBSS方法，两者各有优缺点，但是两种方式测量结果的部分一致性，在一定程度上说明了这两种方法的可靠性。

4 总结与展望

作为目前唯一一种显示活体纤维束轨迹的方式，DTI已广泛应用于科研，但是在临床方面并不能单独作为一项可靠指标，这表明DTI研究过程中仍然存在一些问题。DTI图像成像时分辨率较低、信噪比不高，这都给后续处理带来了很多问题。DTI数据后处理中，VBA方法对配准要求较高，且平滑时没有金标准；应用TBSS方法时，若是FA图有较大的解剖学位移或白质损伤，其骨架化的过程会出现较大失误且选取骨架问题上也一直存在争议；应用纤维束追踪方法，要具备较强的解剖学知识，来确定感兴趣区域，且感兴趣区域分析很耗时，交叉纤维的追踪也一直是一个难以解决的问题。这些问题需要更多研究者投入更多精力来解决。

DTI在医学诊断和治疗方面有很大潜在价值。例如，可以将DTI应用于精确描述水肿、肿瘤和正常大脑结构的范围。传统影像总是低估肿瘤的范围，使治疗未达最佳效果。而DTI可以测量到由于细胞结构和完整性的改变可能引起的水弥散量级和方向性的改变，所以将DTI应用于确定肿瘤范围是一个很好的研究方向[30]。在其他一些可能会导致大脑白质结构和完整性损伤的疾病中，例如上文中提到的阿尔兹海默病、ADHD、弱视、精神分裂症等，DTI指标FA升高、MD下降可以作为诊断和治疗的一种辅助手段。一般情况下，白质纤维束的损伤很可能导致FA较低、MD较高，所以DTI的指标确实有临床意义[31]。DTI的应用应该不仅仅限制于目前所知的几种可能会对大脑白质产生影响的疾病，我们相信通过更多的研究和临床应用，DTI可以应用于更多疾病的诊疗。

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