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神经影像学技术在酒精使用障碍研究与治疗中的应用

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摘　要

酒精使用障碍(AUD)是全球范围内普遍存在的棘手问题，也是物质使用障碍中最为常见的类型。在神经影像学技术不断革新的背景下，多种无创成像技术逐渐兴起，它们被广泛应用于探究饮酒者大脑损伤特征、认知功能缺损情况以及成瘾的神经生物学机制。这些技术包括功能磁共振成像(fMRI)、脑电图(EEG)，以及具有治疗潜力的经颅磁刺激(TMS)和经颅直流电刺激(tDCS)，它们在AUD的诊断、预后评估和治疗中发挥着至关重要的作用。本文系统总结了这些技术的研究应用和相关发现，分析了当前研究的成果及其局限性，并通过整合组内和组间的研究成果，展望了未来研究方向，为更深入的饮酒者研究及治疗提供理论依据和指导。

关键词

酒精使用障碍，功能磁共振成像，脑电图，经颅磁刺激，经颅直流电刺激

Application of Neuroimaging Techniques in the Research and Treatment of Alcohol Use Disorder

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Abstract

Alcohol use disorder (AUD) is a widespread and challenging global issue and the most common type

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of substance use disorder. With continuous advancements in neuroimaging technologies, various non-invasive imaging techniques have emerged and been widely applied to investigate brain damage characteristics, cognitive deficits, and the neurobiological mechanisms of addiction in drinkers. These techniques include functional magnetic resonance imaging (fMRI), electroencephalography (EEG), as well as therapeutic potential methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These technologies play a crucial role in the diagnosis, prognosis assessment, and treatment of AUD. This article systematically summarizes the research applications and relevant findings of these techniques, analyzes current research achievements and limitations, and, by integrating within-group and between-group studies, explores future research directions, providing theoretical support and guidance for deeper research and treatment of individuals with AUD.

Keywords

Alcohol Use Disorder, Functional Magnetic Resonance Imaging, Electroencephalography, Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation

1. 引言

酒精滥用、酗酒和酒精使用障碍(alcohol use disorder, AUD)每年导致超过 300 万人死亡，占全球死亡人数的 6% [1]。酒精对大脑的影响会导致一系列疾病，统称为酒精相关脑损伤(alcohol related brain damage, ARBD) [2]。研究确实表明，酒精的成瘾性与其他毒品如海洛因和可卡因相似[3]，2023 年，世界卫生组织在《柳叶刀》上发表的一份声明强调，对于饮酒而言，没有任何安全剂量。的确，近年来关于酒精的研究发现，早期认为适量饮酒有益健康的结论存在一定的瑕疵，而排除掉这些问题之后发现，酒精其实是从零开始就有毒的，并不存在一个安全量[4] [5]。长期喝酒会导致大脑结构的改变，进一步影响认知、情绪和运动等功能[6]，严重情况下，影响患者的生存质量、威胁其生命安全，并且还会危及他人的生命[7]。目前，多数学者认为饮酒主要是通过多种分子机制在多个器官引起炎症，间接或直接引起中枢神经系统(central nervous system, CNS)损害[8]。急性饮酒会过度激活初级运动皮层神经元，进而导致运动表现下降[9]；反复饮酒则会导致海马齿状回神经元过度激活，导致空间记忆损伤[10]。研究表明，早期对饮酒者进行干预，可减少其发展为阿尔茨海默病(Alzheimer’s disease, AD)以及帕金森病(Parkinson’s disease, PD)的概率[11] [12]。酒精会影响大脑的灰质和白质，也会改变大脑的电生理，然后通过神经可塑性的过程导致成瘾[13]。应用无创神经成像研究饮酒者大脑功能改变、预后及治疗，如功能磁共振成像(functional magnetic resonance imaging, fMRI)、脑电图(electroencephalography, EEG)以及经颅磁刺激(transcranial magnetic stimulation, TMS)、经颅直流电刺激(Transcranial Direct Current Stimulation, tDCS)等。因此，本文旨在系统整理和分析当前关于神经影像学在 ARBD 研究中的进展，探讨各种成像技术的应用以及未来研究的潜在方向，为制定有效的早期干预和治疗策略提供科学依据。

2. 饮酒者脑功能改变

饮酒者的脑功能改变可通过多种神经影像学方法进行综合分析。fMRI 是目前最常用的无创技术之一，而血氧水平依赖(blood oxygen level dependent, BOLD)能够反映大脑的局部血流动力学变化，从而间

接反映神经元的活动[14] [15]。

2.1. 局部脑区活动分析

通过局部一致性(regional homogeneity, ReHo)和低频振荡振幅(amplitude of low frequency fluctuation, ALFF)等分析方法，可以评估脑区自发活动及其与饮酒行为的关联。在饮酒者的脑功能研究中，ReHo 值和 ALFF 值的改变往往揭示了大脑某些区域的活动异常。Liu 等人报道了长期饮酒者前额叶－顶叶－小脑回路 ALFF 的异常幅度[16]。进一步研究表明，饮酒模式与大脑的 ReHo 和低频振幅分数(fractional ALFF, fALFF)有显著关联，这可能会影响认知功能[17]。

2.2. 静态功能连接分析

然而，单靠局部分析不足以全面揭示饮酒对脑功能的影响。基于体素水平的度中心度(degree centrality, DC)方法可以用来评估大脑不同区域之间的功能连接强度。DC 分析方法发现，男性 AUD 患者左侧中央前回的 DC 值明显高于对照组，且左侧脑区的差异数量和总体积明显多于右侧，这进一步探索酒精成瘾及其后果的神经生物学机制[18]。此外，功能连接(functional connectivity, FC)方法进一步揭示了大脑各区域间的互动与协调问题。利用静息态功能连接(resting-state functional connectivity, rsFC)研究[19]表明，左侧中央前回与内侧眶额皮质以及与疼痛调节相关的导水管周围灰质有功能连接，这与饮酒的调控密切相关。另一项研究[20]表明，随着饮酒量的增加，杏仁核与前额叶之间的功能连接减弱。Ruan 等人[21]的研究结合了 DC 与基于种子点的 FC 分析，发现 AUD 患者的 FC 变化与症状严重程度有关，这为理解 AUD 的神经机制提供了新的线索。

2.3. 动态功能连接分析

研究发现，AUD 患者的动态功能连接(dynamic functional connectivity, dFC)状态比健康对照组更少，且转换频率降低，表明饮酒者的大脑在不同功能状态间的切换能力下降[22]。此外，酒精依赖患者在静息态下的三重网络(Triple Network Model)，即默认模式网络(default mode network, DMN)、突显网络(salience network, SN)和中央执行网络(central executive network, CEN)，其动态功能连接特征发生异常，表现为网络状态的稳定性下降、转换频率降低，以及 CEN 内部功能连接的增强[23]。胎儿期酒精暴露(prenatal alcohol exposure, PAE)导致胎儿酒精谱系障碍(fetal alcohol spectrum disorder, FASD)的静息态动态功能网络连接(resting-state dynamic functional network connectivity, dFNC)发生异常变化，相较于健康对照组，他们表现出更高的动态流动性和动态范围，并更频繁地处于功能连接异常的状态[24]。这些变化可能影响认知功能，并进一步揭示了 PAE 对大脑功能网络的全球性影响。

2.4. 独立成分分析与三重网络模型

独立成分分析(independent components analysis, ICA)是一种完全数据驱动的方法，能够将 BOLD 信号分解为一组空间独立的成分，无需预定义种子区域，因此被广泛应用于识别和定位大脑中的不同功能网络[15] [25]。先前的一项研究[26]表明，急性酒精暴露会影响 DMN 的静息功能连接，这与记忆编码密切相关。进一步的多模态研究表明，饮酒者的 DMN 和突出网络(salience network, SN)结构异常与记忆力减退有关[27]。此外，饮酒量增加与旁扣带回的 DMN 连接性增强和执行控制网络(executive control network, ECN)连接性减弱[28]。与戒酒者相比，酗酒者在 ECN 中的功能连接性显著增强[29]。AUD 患者在静息态下三重网络(CEN, DMN, SN)的功能连接发生了异常增强，尤其是在 CEN 内部及其与 DMN 和 SN 之间的连接[30]，这可能反映了 AUD 患者在认知控制、注意力分配及自我相关处理方面的异常。

2.5. 结构网络分析与拓扑变化

基于图论的脑网络分析提供了一种全局视角，将大脑视为一个互相连接的复杂网络，用于揭示整体大脑网络的连通性和拓扑结构变化。Zhang 等人[31]发现急性饮酒会显著影响大脑网络的功能连接，这可能反映出急性饮酒的生理效应。Lee 等人[32]进一步通过图论分析发现，AUD 患者的整体脑网络节点效率较低，表明其功能连接受损。

此外，酒精依赖患者的大脑结构共变网络的拓扑组织发生异常，主要表现为全局信息传递效率降低和局部关键脑区的连接性受损[33]。酒精依赖会导致脑结构网络的稳定性下降，主要表现为全局和局部效率降低，特别是在涉及运动控制、认知控制和自我认知的关键网络中[32]。这种网络连通性损害可能降低信息处理的灵活性和效率，使得患者在局部脑区功能受损时更难进行有效补偿，进而影响认知和行为功能。

对于早期戒酒的 AUD 患者，研究发现其整体功能连接仍然较弱[34]。而戒酒一年者在全局脑网络组织方面与对照组没有显著差异[35]，说明戒酒时间延长可恢复一定程度的正常脑功能。

2.6. 动脉自旋标记成像分析

此外，动脉自旋标记成像(arterial spin labeling, ASL)是一种非侵入性 MRI 技术，它使用内源性动脉血作为动态示踪剂来量化器官的组织灌注。急性饮酒的 ASL 研究报告称，大脑前部区域灌注增加，尤其是额叶区域[36] [37]。尽管急性酒精摄入和慢性饮酒都会选择性地影响额叶皮质，然而，对于慢性酗酒者而言，脑灌注的结果则有所不同。在 AUD 患者中，额叶区域的脑血流量(cerebral blood flow, CBF)减少，并且岛叶的 CBF 与大量饮酒呈负相关[38]。进一步研究显示，饮酒程度与显著影响注意和情绪调节的 SN 关键节点的 CBF 也呈负相关[39]。这表明，慢性酗酒可能导致神经功能的改变，从而影响情绪和认知能力。这些关于饮酒者脑功能改变的研究，运用多种 fMRI 分析方法和 ASL 技术，从不同角度展示了饮酒对大脑功能的影响。但目前研究在研究方法的统一性和研究结果的普适性上存在不足。未来可加强多中心合作研究，采用标准化的实验设计和分析流程，整合多模态影像数据，深入研究脑功能改变与饮酒行为、认知损害之间的动态关系，以及戒酒对脑功能恢复的影响机制。

3. EEG 在饮酒者中的应用

EEG 是一种通过头皮电极实时记录大脑电活动的技术，近年来广泛应用于饮酒者的脑功能研究，尤其是探讨酒精成瘾、认知功能受损及神经电活动异常的相关现象。EEG 的事件相关脑电位(eventrelated potentials, ERPs)能够有效评估大脑活动，特别是 P3 波已被证明是理解酒精相关认知的重要工具[40]。在 EEG、ERPs 和事件相关振荡(event-related oscillations, EROs)的研究中，酗酒者在处理目标和非目标刺激时表现出较小的 P3 波幅，表明他们的中枢神经系统抑制能力较弱[41]。这些现象可能反映出饮酒对神经传递功能，特别是与认知控制和执行功能相关的神经环路的破坏。此外，急性酒精中毒削弱了对酒精相关线索的神经反应，进一步降低了 P3 波幅，提示酒精摄入减弱了目标刺激的神经处理能力[42]。Cofresí 等人[43]研究发现，女性饮酒者的 P3 波幅下降程度通常低于男性，可能反映了性别在酒精相关神经损伤中的差异。这一性别差异引发了对酒精对男性和女性大脑影响机制的进一步研究需求，有助于制定更具性别针对性的干预措施。进一步研究发现 P3 波幅与酒精使用的程度(如血液酒精浓度和累积饮酒量)呈正相关[44]。

近年来，基于 EEG 数据的机器学习方法在筛查 AUD 患者方面展现了巨大潜力。通过将 EEG 信号的特征输入机器学习算法，可以显著提高对酒精使用障碍的诊断准确性。研究表明，结合快速傅立叶变换、卷积神经网络和长短期记忆网络的深度学习架构，能够以超过 90%的准确率识别酗酒者[45]。这种方法为

未来基于 EEG 的自动化诊断工具提供了可能性，并为精准治疗提供了新的方向。未来的研究可以进一步优化 EEG 信号的处理和分析，尤其是与其他技术的结合。例如，脑磁图(Magnetoencephalography, MEG)与 EEG 的同步记录可以更好地捕捉深层脑区的活动，提高脑活动的空间分辨率[46]。除此之外，整合 EEG 数据的空间、时间和频率特征，以及通过多电极记录更多脑区的活动，将为理解饮酒者的大脑功能提供更全面的信息。EEG 技术在饮酒者脑功能研究中取得了一定成果，揭示了 P3 波幅与酒精使用的关联以及性别差异，还开拓了基于机器学习的诊断新思路。不过，目前 EEG 研究在信号解读的复杂性和空间分辨率方面存在局限。未来应着力解决这些问题，通过与其他技术融合，挖掘更多潜在生物标志物，提升对饮酒者大脑功能异常的理解和诊断能力。

4. 酒精成瘾的无创神经技术治疗应用

由于药物治疗效果有限，许多患者尚未准备好戒酒，因此他们对当前治疗中的戒酒目标缺乏兴趣或动力[47] [48]。在这种情况下，一种有趣的替代方法在成瘾研究中引起了越来越多的兴趣，即使用非侵入性电刺激——经颅磁刺激(transcranial magnetic stimulation, TMS)和经颅直流电刺激(transcranial direct current stimulation, tDCS)。TMS 和 tDCS 最近成为一种有前途的、无创的基于神经回路的 AUD 治疗方法[49]。

4.1. TMS

TMS 是一种通过电磁线圈产生磁场，在大脑中引发局部电流，从而改变神经活动的非侵入性技术。TMS 已经广泛应用于物质成瘾、多种神经和精神疾病的治疗[50] [51]。其中，以背外侧前额叶皮层(dorsolateral prefrontal cortex, DLPFC)为靶点的 TMS 治疗，在酒精成瘾患者中显示出较好的效果[52]。DLPFC 在执行功能和冲动控制中发挥关键作用，TMS 通过调节 DLPFC 的神经活动，有助于改善成瘾者的决策能力，减少酒精渴求和复发风险[53]。当在多个序列中施加脉冲时，其被称为重复 TMS (repetitive TMS, rTMS)。rTMS 对单侧 DLPFC 的刺激已被证明能在一定程度上减少酒精渴求[54]。其中，一种新型 rTMS 模式——θ 波爆发刺激(theta burst stimulation, TBS)也被研究用于治疗 AUD 患者，McCalley 等人[55]的研究显示，TBS 对 DLPFC 的刺激可以提高治疗的持久性并减少复发率。临床研究中，DLPFC 尤其是右侧 DLPFC，作为高频 rTMS (High Frequency rTMS, HF-rTMS)的靶点，在治疗酒精成瘾方面显示出前景[56]。HF-rTMS 对右侧 DLPFC 的刺激显著减少了酒精摄入量[57]，然而，左侧 DLPFC 的 HF-rTMS 在减少渴望和酒精摄入方面未显示出显著效果[51] [58]。尽管 HF-rTMS 对右侧 DLPFC 的疗效较为突出，但其长期效果仍存在争议。最近的研究[57]指出，接受 HF-rTMS 治疗的患者在 3 个月的随访中表现出显著疗效，HF-rTMS 对右侧 DLPFC 的疗效最为显著。而另一项研究，则表明，在 6 个月和 12 个月的随访中，HF-rTMS 对 AUD 患者的长期疗效与对照组无显著差异[59]。这种疗效的不稳定性可能与大脑的代偿机制有关。DLPFC 的兴奋性增强可能会引起其他成瘾相关脑区的适应性变化，从而影响 TMS 的长期治疗效果。此外，TMS 能否诱导持久的突触可塑性仍需进一步研究。未来可以探索基于个体神经兴奋性的优化策略。例如，先利用单脉冲 TMS 测定运动皮层静息运动阈值，再据此调整 TMS 强度。此外，可结合 EEG 神经反馈技术，实时监测 DLPFC 的活动状态，并动态调节 TMS 参数，以提高治疗的个性化效果。

4.2. tDCS

tDCS 是一种通过在头皮上安放电极并传递低强度直流电流来调节大脑皮层神经元兴奋性的无创神经调节技术。与 TMS 相比，tDCS 设备更为简单且便携，因此能够方便患者在家中自行使用[56]。近年来，tDCS 在 AUD 治疗中的应用得到了初步验证，尤其是在调节前额叶皮层功能方面。

Holla 等人的研究发现，tDCS 能够提高 AUD 患者的全脑网络效率，这一能力的提升与患者维持戒断

的能力密切相关[60]。此外，部分研究使用了 2 mA 电流 tDCS 刺激发现，tDCS 能够有效减少酒精渴望[61] [62]。但有些研究表示[54] [63]-[65]，tDCS 在减少对酒精的渴望方面是无效的。这种疗效的不一致可能与实验设计的差异有关，包括刺激强度、持续时间以及受试者的个体神经状态。例如，长期酗酒者可能存在 DLPFC 功能受损，导致 tDCS 的疗效下降。此外，tDCS 的电流扩散范围较广，可能影响多个脑区，降低刺激的靶向性。尽管疗效存在争议，最新的荟萃分析仍支持左侧 DLPFC 区域使用 2 mA 电流的 tDCS 作为治疗 AUD 的有效靶点[66]。未来研究可进一步评估更高强度(如 3 mA)的 tDCS，以优化治疗参数，但仍需关注个体耐受性及长期安全性。此外，还可尝试交替电流刺激，通过个性化的脑区频率匹配提高对成瘾网络的调控效果。复发在 AUD 患者的治疗中十分常见，因此许多研究将 tDCS 用于预防复发。多项研究[60] [67] [68]采用 2 mA 电流刺激左侧 DLPFC，并在大多数情况下发现 tDCS 显著减少了复发率。这一作用机制可能与 tDCS 对前额叶－成瘾网络连接性的调节有关。虽然大多数研究支持 tDCS 在减少渴望和复发中的作用，但仍有部分研究未能发现 tDCS 显著优于假刺激的效果。例如，Witkiewitz 等人[69]指出，治疗酗酒，tDCS 的效果并未显著优于基于正念的复发预防。尽管如此，最新的研究[70]表明，双侧 DLPFC 的 tDCS 刺激是一种安全且有效地降低酒精渴望的方式。

DLPFC 是 TMS/tDCS 最常用的靶点，但个体间解剖结构的差异可能影响刺激的精准度。当前 TMS/tDCS 的刺激靶点通常基于标准坐标，但个体间解剖和功能存在较大差异。因此，未来研究可以结合 fMRI 功能连接分析，优化 DLPFC 的刺激靶区，特别是与成瘾相关的脑网络(如 DMN、CEN、SN)的关键区域。此外，有研究[71]表明，皮质杏仁核在酒精依赖的神经机制中起到重要作用，可能是另一个值得探索的治疗靶点。

总体而言，tDCS 与 TMS 等无创脑刺激技术在 AUD 治疗中的应用仍具有很大潜力，但目前仍面临疗效不稳定、长期效果不确定以及研究结果不一致等问题。未来可结合闭环调控 TMS/tDCS 技术，利用 EEG 监测个体神经活动，动态调整刺激强度和时间，以提高个性化治疗效果。

5. 结论和未来展望

通过这些无创成像手段，越来越多的研究揭示了酒精依赖患者功能的改变，为酗酒、AUD 患者的早期诊断、治疗、疗效评估和戒酒提供了神经影像学证据。这些技术的应用不仅揭示了酒精对大脑长期损伤的神经机制，为未来的治疗策略提供了新的方向。尽管已有显著进展，仍有许多问题尚待解决。未来的研究可以进一步优化现有技术，并将多种成像和刺激手段结合使用，以提高对复杂大脑网络和行为之间关联的理解。此外，研究需要更大规模、长时间随访的临床试验，以验证 TMS 和 tDCS 等新兴技术的长期疗效和安全性。通过跨学科合作，结合遗传学、药理学和神经成像的多维度研究，我们或能更全面地揭示酒精成瘾的病理机制，为个性化治疗提供更精确的理论依据。总体而言，神经影像学在酒精使用障碍研究中成果颇丰，但仍存在诸多挑战。未来需从技术优化、多技术融合、扩大临床研究规模和跨学科合作等方面深入探索，以实现对酒精使用障碍从机制研究到临床治疗的全面突破，为改善患者健康状况提供有力支持。

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