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物质成瘾所伴随的认知功能缺陷及其神经基础

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摘要 物质滥用和成瘾是当今世界最严重的公共卫生问题之一, 禁毒与戒毒已成为全球关注的社会热点. 根据DSM-5定义, 物质成瘾是一种慢性复发性精神疾病, 表现为强迫性药物寻求、无法控制药物使用而无视其潜在的严重危害. 超过80%的成瘾个体没有寻求治疗, 这部分反映出物质成瘾个体存在认知功能方面的缺陷与障碍. 以此为出发点, 本研究回顾了近年来关于物质成瘾者在注意、抑制控制、决策和内感受等方面认知功能缺陷的研究, 总结了行为和神经影像学方面的成果, 探讨和论证物质成瘾背后的认知神经机制, 以便更准确地了解物质成瘾的成因、发展、戒断和复发的本质. 最后, 本研究提出未来的相关研究应致力于推动多技术融合, 关注共病问题, 构建和完善生物标记, 开发基于脑的干预方法, 以便深化该领域的研究, 有助于完善成瘾病人的干预与治疗机制.

关键词 物质成瘾, 注意, 抑制控制, 决策, 内感受

物质成瘾是一种对某种物质的持续性使用所引起的周期性或慢性中毒状态, 其核心特征为个体强迫性、无法控制地用药和觅药, 而忽视其潜在严重危害的行为. 比如, 成瘾个体变得只关注于获得和使用药物, 而不管身体状况的下滑、人际关系的破裂甚至事业的失败[1]. 根据美国精神病学会(American Psychiatric Association, APA)在精神疾病诊断和统计手册第5版[2](The Diagnostic and Statistical Manual of Mental Disorders, DSM-5)中的描述, 物质使用障碍是一种个体对物质使用的不良适应行为, 会导致个体出现明显的认知、行为和生理上的问题, 并且个体会不计后果地持续使用, 其关键特征为: (1) 无法控制地用药以及在熟悉用药环境下容易产生药物渴求; (2) 日常生活以药物使用为中心, 学业事业的失败以及人际关系的破裂; (3) 持续用药而忽视已有的周期性身心问题; (4) 药物耐受性的产生, 以及一旦无法获得药物就表现出的戒断症状. DSM-5中还按照成瘾物质的药理学性质进行了简单分类, 将易成瘾的物质分为了以下10类: 酒精、咖啡、大麻、致幻剂、吸入剂、阿片类药物、镇静药、安眠药、抗抑郁药、兴奋剂、烟草, 以及其他物质.

虽然每种物质的药理作用和成瘾途径不尽相同[3,4], 但纵观中外关于成瘾背后认知机制的研究却一致地发现, 无论是单一的物质滥用还是多药滥用, 都会不同程度地损伤个体的注意[5~7]、抑制控制[8~10]、决策[11]、内感受[12,13]等多方面的认知能力. 与之对应, 美国国立健康研究院下属的国家药物滥用研究所(National Institute of Drug Abuse, NIDA)所长Volkow等人[14,15]也多次提到"成瘾是一种脑部疾病", 无论何种物质成瘾, 虽然其背后的分子机制不同, 但

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都会影响人类一些普遍的高级认知加工过程，如注意、抑制控制等[16~18]. 而采用脑成像为技术手段的研究表明，大多数成瘾药物都是通过促进大脑边缘系统的多巴胺释放急增而发挥强化作用，产生欣快感，继而影响其他神经递质系统，导致神经元可塑性发生改变，致使奖赏、动机、学习、记忆、抑制控制等神经环路发生显著变化，从而改变注意、抑制控制、决策和内感受等方面的行为特点[19]. 进一步的研究发现，长期的药物使用会造成这些能力对应的脑区结构和功能的改变，并且脑结构和功能的改变会导致相应的认知功能损伤，而认知功能的下降反过来会进一步加剧成瘾程度，形成恶性循环，同时阻碍戒断治疗的顺利进行.

因此，本文从考察物质成瘾个体的认知加工角度出发，分别介绍了成瘾个体在注意、抑制控制、决策和内感受等方面的特征以及其行为学和神经影像学的研究证据，阐述和分析物质成瘾引起的认知功能方面的缺陷及其背后的神经基础，并将之整合到物质成瘾理论模型中，最后提出今后研究的方向. 这样的分析可以加深人们对物质成瘾的成因、发展、戒断、复发机制的了解，同时更有助于我们找到更加科学合理有针对性的干预和治疗手段，帮助物质成瘾者在一定程度上恢复和提高认知水平，降低复吸率.

1 物质成瘾者的注意功能障碍研究

注意是指选择性地加工一项特定刺激而忽视其他无关刺激的能力[20]. 研究表明，物质成瘾者往往存在一定的注意能力缺陷，表现为在药物环境中易被药物相关线索吸引以及对药物线索注意的持续时间增加等[21]. 在物质成瘾领域，研究者们一般用注意偏差范式来研究注意行为. 成瘾个体的注意偏差是指药物相关线索更易于获取药物成瘾者注意的现象[22~24]；一般说来，药物相关线索会自动攫取成瘾者的注意力，并引起无意识的觅药行为[23]. 它是物质成瘾的核心特征之一，与物质成瘾的维持与复吸有着重要的联系[22].

1.1 行为学研究

行为上已有大量研究证明了物质成瘾者存在一定的注意偏差，而这种注意偏差是由两方面因素导致的：一方面是由于其注意更容易被药物相关刺激所吸引；另一方面是药物相关的刺激影响了注意维持的时间或注意解除的能力，使得成瘾者的注意力在这些刺激上停留的时间较长. 尼古丁研究表明，香烟能使成瘾个体在注意的早期定位及后期维持方面出现偏差，即吸烟者的注意更容易被香烟刺激吸引，且在香烟刺激上停留时间更长[21,25~27]，而这可能是由于其缺乏调整注意加工的能力造成的[28]；同时，药物滥用会强化个体对药物相关刺激的反应，引起个体对药物刺激的注意偏向，并且最终导致个体的一般认知功能(如抑制控制、言语和抽象能力)损伤[29]；此外，研究表明，药物相关刺激捕获注意的能力在成瘾、渴求和复吸中也发挥着重要作用[27,30~33].

物质成瘾的注意偏向会受到诸多因素的影响，如冲动性[34]、渴求水平[35]、期望[34]、压力水平[36,37]和治疗寻求意愿[38]等. 研究发现，酗酒者对中性刺激与食物相关自然奖赏物的反应并无显著差异，但对酒精相关线索存在更强的认知偏差，同时这种偏差程度与其渴求水平成正相关，表明即使在面对一般自然奖赏物时，药物线索仍更能够捕获个体的注意，注意偏差程度会受到渴求水平的影响[39]. 另外，干预研究发现药物戒断者会表现出注意远离药物相关刺激，表明成功的戒断治疗与注意远离药物有关，这种注意远离现象可能是一种对压力效应的抵抗[37].

1.2 神经影像学研究

近年来神经影像学研究显示物质成瘾者对药物相关刺激的注意偏差与认知控制网络(前额叶、前扣带回等)和情绪加工相关脑网络(杏仁核、脑岛、伏隔核等)的异常有关；研究者认为，当认知控制网络的活动强度不足以抵抗共存的情绪/奖赏区的活动增强时，成瘾个体的注意更易于被药物相关刺激攫取[34]. 研究发现，药物线索可以显著诱发个体渴求相关脑区(如脑岛、伏隔核等)的强烈活动，此时个体负责自上而下注意加工的相关脑区(如背外侧前额叶、前扣带回、顶叶等)就需要调动更多的认知资源去处理当前的认知任务[40]；同时，内感受相关脑区(如脑岛、前扣带回)与认知控制网络之间的功能连接程度下降，表明认知控制网络对情绪等相关脑网络的调节能力下降，即药物线索致使个体将注意从外部刺激转向自身的内部状态和情绪记忆，从而产生渴求感[41]，这也可能是成瘾个体会出现复吸的原因之一. 此外，反应抑制及易感性受损模型(impaired response inhibition and salience attribution, I-RISA)[42]认为前扣带

回及眶额叶皮层在对药物线索的易感性中发挥着重要作用; 药物线索足够引起额叶、颞叶及皮下神经核团等脑区的强烈活动[43], 而背侧前扣带回的活动强度也与复吸有关[44], 表明前扣带回及眶额叶的活动异常可能是药物成瘾者对药物线索的注意偏向的神经基础, 对前扣带回和眶额叶进行干预可能有助于增强自上而下的监控和情绪调节, 从而减少个体的冲动和强迫性用药行为[45,46].

成瘾个体的药物滥用与其对药物线索的注意偏向之间存在十分紧密的联系, 药物滥用个体无论是在发展期还是戒断期均存在明显的注意偏向的问题; 药物相关线索可以诱发个体与药物奖赏以及动机相关的中脑-皮层-边缘网络的激活, 而这种异常加工足以引起对药物相关刺激的注意调整, 因此额叶-边缘系统的神经适应性改变可能是药物趋向偏差的基础. 然而, 我们对物质成瘾者对药物线索的注意偏向的进一步的认知和神经基础并不十分明晰, 如个体对性、食物等高唤醒的情绪性突显刺激同样表现出较强的注意偏差, 这里的注意偏差与对药物相关刺激的注意偏差是否具有相似的神经基础?

2 物质成瘾者的抑制控制功能障碍研究

抑制控制是指个体在追求认知表征目标时抑制无关或干扰刺激以及冲动的能力[47], 并以此抑制优势反应和习惯, 灵活地调节适当的行为以满足复杂任务的要求和不断变化的环境[48], 因此, 抑制控制是一种对思考加工和生活都至关重要的执行功能之一. 长期滥用药物会导致个体的抑制控制能力受损, 使得成瘾个体往往表现出行为抑制能力差、反应迟钝、冲动性强、易怒以及在特定药物相关环境下难以克制觅药行为等特点.

2.1 行为学研究

尽管现有的行为研究关于不同物质成瘾者的抑制控制能力下降的结论不太一致, 但在药物线索下, 不同药物滥用者均会出现抑制能力损伤的现象, 这种损伤一方面是由于抑制无关信息的能力在一定程度上受损, 另一方面是执行监控能力不足造成的. 研究发现, 吸烟者抑制控制能力与日常吸烟量有关[49], 同时受戒断时间影响[50], 表明抑制优势反应能力不足已成为吸烟者的一种重要特征. 对酒精[51,52]、海洛因[51,53]、阿片类药物[37]、可卡因[8,54,55]及冰毒[56~58]等研究发现成瘾个体存在认知灵活性以及冲突抑制能力的缺陷. 例如: 可卡因患者在抑制优势反应时表现出较差的操作监控能力, 表明可卡因患者抑制控制损伤可能是由于其对刺激的操作监控不足所致[55]. 因此, 物质成瘾者的反应抑制问题可能是一种源于抑制无关信息能力受损的反应选择缺陷, 这也与临床表现的注意力分散现象一致[57], 而抑制控制能力(如对药物渴求的抑制控制)的减弱可能是其开始并持续使用药物甚至复吸药物的重要因素[59].

2.2 神经影像学研究

关于物质成瘾者抑制控制的神经影像学研究一致认为抑制控制能力的损伤与前额叶-纹状体-丘脑环路(特别是前额叶)的活动异常有关. 前额叶环路抑制控制能力相对不足会导致个体无法抑制自己的行为, 做出不当的行为选择, 加之物质成瘾者对药物寻求的冲动性及强迫性, 两者结合在一起就能解释为何个体会不顾负性后果继续使用成瘾性物质. 香烟[60~63]、酒精[64]、可卡因[65~67]、大麻[68,69]、海洛因[70,71]等研究均发现, 在抑制优势反应时, 成瘾个体背外侧前额叶、眶额叶、前扣带回等认知控制相关脑区活动不足, 而纹状体、杏仁核以及脑岛等活动增强; 背外侧前额叶涉及对潜在后果的整合与目标导向行为, 被认为是抑制控制功能最重要的脑区, 扣带回与错误监控等能力密切相关, 脑岛被认为参与线索渴求以及药物情绪记忆加工, 而杏仁核一直被视为是冲动性的关键结构, 这些脑区构成冲动的神经环路, 因此该环路的活动异常可能是成瘾者抑制功能损伤的潜在神经基础[70].

尽管目前观点一致认为, 前额叶-纹状体-丘脑环路的活动异常可能是致使其抑制控制能力损伤的神经基础, 然而我们对其认知与神经基础与其他因素的联系尚不十分明确, 比如: 新颖寻求特质和冲动特质的个体更多地会表现出抑制控制等问题行为, 那么这些人格特质与成瘾人群的抑制损伤以及脑功能异常之间是否存在一定的关系? 因此, 我们仍需采用不同的技术手段、研究范式去深化物质成瘾中抑制控制缺陷在人格、行为、认知、神经及分子方面的机制.

3 物质成瘾者的决策功能障碍研究

决策是指在有多种选择的情况下选择一种方案

的过程[72]. 一般个体在面临多重选择的情况下, 往往会通过评估与权衡潜在选项的收益(或损失)可能以及付出成本, 然后偏向于低风险高收益的选择; 而药物成瘾者被认为存在决策障碍, 易做出不利的决策, 选择继续药物寻求, 主要表现为: 为了眼前较小利益而放弃追求长期较大收益的短视行为、容易做出冲动决策、无法根据已有经验调整决策策略、不能根据收益可能性做出最佳选择、不能调整长短期收益以实现利益最大化等[73].

3.1 行为学研究

决策加工涉及环境刺激的奖赏价值或者情感效价, 评估潜在选项的奖赏或惩罚, 整合潜在积极或消极结果信息, 并最终做出选择行为等过程. 研究表明, 长期物质滥用者的决策受损一方面是由于对未来获益的显著折扣(即在面对即时较小收益和未来较大收益, 对未来奖赏的主观价值随时间的增加而明显下降)和对选择的调节能力降低, 一方面是由于整合奖罚信息能力减弱而无法做出最优选择. 物质成瘾者在决策时有更高的风险倾向性[74,75]以及对未来获益有更高的时间折扣[75~79], 同时这种行为倾向会受戒断时间[80]、成瘾程度[81~83]、性别[84]、以及家庭环境与遗传[85]等因素的影响. 然而另有研究表明, 成瘾者较高的时间折扣可能反映的是一种外化的抑制能力缺陷[86]; 如可卡因患者面对金钱(二级奖赏物)与可卡因时无一例外地选择了进行可卡因注射[87], 而在赌博测验中会更多地选择较大赌注但损失风险性同样大的不利选项, 表现出有更强的冲动性和更弱的行为抑制能力[88].

3.2 神经影像学研究

结合前人的研究成果, Noël等人[89]系统地阐述了决策障碍是由三个独立但又相互影响的系统其功能受损所引起的; 冲动性系统(杏仁核、纹状体等)反映人最本质的一面, 受外界刺激的直接影响, 在物质成瘾者中一般表现为过度反应. 反射性系统(前扣带回、前额叶、海马等)促使人们根据长期的结果做出决策, 在物质成瘾者中表现为反应降低. 脑岛系统是对前两个系统进行平衡的系统, 主要受当前身体状态的影响, 比如在戒断情况下, 它可以增强冲动系统的活动, 劫持目标驱动的认知资源, 从而致使反射性系统活动降低, 形成冲动行为和决策. 根据这一理论, 研究发现, 在决策加工时, 物质成瘾者的情绪与动机相关脑区(杏仁核、脑岛等)过度活跃[90], 但与奖罚相关的皮下结构(纹状体等)以及前额叶神经网络对得失反馈的敏感性异常[91], 表明情绪与动机相关脑区的过度反应以及策略发展阶段前额叶对负性反馈敏感的反应不足可能是成瘾者往往会做出糟糕决策的原因[92,93]. 简而言之, 药物成瘾者负责执行控制及监控的背外侧前额叶、前扣带回等脑区功能异常可能导致延迟折扣增加, 而负责加工药物奖赏价值和结果预期的眶额叶以及杏仁核等脑区的功能异常可能导致做出冲动和冒险决策, 因此, “冲动性系统”、“反射性系统”以及脑岛系统之间的失衡是造成其决策能力受损的神经基础[94].

物质成瘾者忽视长远的有利选择而短视地选择追求吸食毒品的奖赏快感, 部分解释了成瘾的机制. 然而决策系统是非常复杂的, 虽然我们对其潜在神经基础的探索取得了巨大的进步, 但对成瘾个体在决策的不同阶段(如: 在任务前期损失巨大的情况下, 物质成瘾者会选择什么样的决策策略)的认知机制与神经基础研究较少, 因此我们仍需进一步细化成瘾人群在不同情境、不同阶段的决策过程; 最后, 成瘾人群行为遗传学研究是探索成瘾者决策障碍形成机制的一个新的有效途径.

4 物质成瘾者的内感受功能障碍研究

内感受是指对整个躯体(而不仅仅是内脏)的生理状态的感知[95], 通过接收、加工和整合外部刺激与躯体相关的信号, 影响动机行为, 是一种重要的促进个体趋近或回避药物滥用的加工过程[96]. 个体对刺激的趋近或回避行为都是以维持个体内在的平衡为宗旨的[96], 这个平衡状态被称作内稳态[97]. 机体可以通过内感受监控自身的内部状态, 自动调节行为以完成趋利避害的环境适应功能; 但成瘾药物的使用和戒断可以对内感受系统产生影响, 造成对机体自身内部状态的感知失调, 导致情绪和动机发生改变, 调控成瘾行为的复发[98].

4.1 行为学研究

尽管物质成瘾者内感受功能方面的直接行为研究较少, 但是我们仍可以从两个方面的研究间接地证实物质成瘾者的内感受功能失调. 首先, 内感受线索可以作为一种强烈、特定的条件刺激, 诱发多巴胺

的释放从而影响药物寻求行为[99]. 例如, 在动物成瘾模型的研究中, 使用可卡因钾碘化物(一种四级可卡因类似物, 只会作用于外周系统, 无法越过血脑屏障而作用于大脑)作用于成瘾小鼠, 发现小鼠中脑被盖区的谷氨酸与多巴胺的释放及可卡因觅药行为的出现[100]. 其次, 成瘾个体主观情绪体验(如药物渴求)与生理活动强度之间不匹配[99]. 例如, 相对一般饮酒者, 酒精成瘾者在压力意象情景中的渴求水平更高, 但皮质醇反应却较低[101]; 一般饮酒者的心率反应与主观渴求显著相关, 而酒精成瘾者心率与渴求之间的相关并不显著, 因此, 成瘾者对生理变化与情绪体验的不一致, 表明内感受敏感性的变化可能与对药物刺激所产生的情绪信息的错误感知有关[99].

4.2 神经影像学研究

近年越来越多的神经影像学证据表明物质成瘾个体的内感受加工系统(尤其是脑岛和前扣带回)存在功能障碍. 脑岛作为内感受加工的神经系统核心, 具有前中后功能上的分化, 躯体感觉相关信息首先进入后脑岛, 并与中脑岛的内部状态信息进行整合, 然后在前脑岛再表征为一种复杂的感觉状态[102]. 研究表明, 药物成瘾者在认知控制加工中脑岛活动减弱[103], 而在药物线索反应和奖赏相关加工过程中脑岛的活动增强[104~106]. 同时, 脑岛的活动与个体是否复吸有着直接而紧密的联系[107], 脑损伤研究发现, 相比其他脑区损伤的吸烟者, 脑岛损伤的吸烟者更有可能轻易、迅速、无复吸和无渴求地戒除烟瘾; 研究者在随访过程中发现, 一名经历了左脑岛中风后即时戒烟的被试, 陈述到“身体忘记了吸烟的渴求”[13], 表明内感受系统特别是脑岛在成瘾的维持和复吸中发挥着至关重要的作用.

目前人们已经开始注意到内感受功能在成瘾的产生与维持中有着重要作用, 但仍然没有直接的行为或者影像研究证明其在成瘾中的相关作用与神经基础. 因此, 我们仍需要使用更有效的范式和手段, 更细致地探索内感受与其他认知能力之间的交互作用等, 比如: 决策能力是否会受到以及如何受到躯体感知能力的影响? 这将有助于我们更系统更清晰地认识内感受系统的功能, 同时促进我们了解到内感受系统尤其是脑岛在成瘾行为中所发挥的潜在作用.

5 物质成瘾的认知模型

近年来关于物质成瘾的认知缺陷方面的国内外研究不断增多, 对成瘾的认知神经基础也有不同的理论解释, 如早期Solomon提出“反向过程学说” (opponent-process theory)[108]、Robinson和Berridge的“动机-敏化学说” (incentive-sensitization theory)[109,110], 以及Volkow等人[16~18]整合前人结论与神经影像学发现, 基于认知神经回路提出的奖赏-记忆-动机-执行控制环路的“多重神经回路模型”. 多重神经回路模型(图1)认为, 成瘾是由于奖赏、记忆、动机决策、执行控制、内感受以及情绪等环路之间对信息加工和整合的失衡造成的; 其中, 奖赏环路主要涉及伏隔核、中脑腹侧被盖区以及腹侧苍白球等; 记忆环路主要涉及杏仁核、内侧眶额叶、海马及背侧纹状体等脑区; 执行控制涉及背外侧前额叶、前扣带回、额下回及外侧眶额叶等; 内感受环路主要由脑岛、丘脑及前扣带回组成; 而动机环路主要由内侧眶额叶、腹侧前扣带回、背侧纹状体、黑质致密区以及运动区等组成. 在正常情况下, 这些环路以一种平衡的方式整合来自个体内外部的信息, 并促使个体产生合适的行为; 但成瘾个体在对药物相关刺激进行加工时, 奖赏、动机及记忆环路会挣脱执行控制环路对其的调节, 同时, 内感受环路与情绪环路也会进一步削弱执行控制环路的控制作用, 从而致使个体选择继续用药而无视这种行为选择所带来的潜在危害; 这也就解释了成瘾个体为何出现对药物刺激的注意偏向、抑制控制能力下降以及不合理决策等行为.

6 总结和展望

随着物理学与生物学的发展, 一些越来越先进的无损、可量化的神经影像学方法和技术被应用于心理学的研究中, 如EEG (electroencephalography), fMRI (functional Magnetic Resonance Imaging) 及 fNIRS (functional Near-Infrared Spectroscopy)等. 以此形成的认知神经科学也得到了前所未有的迅速发展. 相对于传统心理学研究, 认知神经科学在先进仪器的帮助下对于揭示物质成瘾更深层的心理机制与神经基础方面更具有优势, 加深了我们对成瘾的认识和理解, 使诊断标准和干预措施更准确、具体、且行之有效. 尽管如此, 目前的研究仍然存在一些问题, 未来的研究有必要在以下四个方面进行探索.

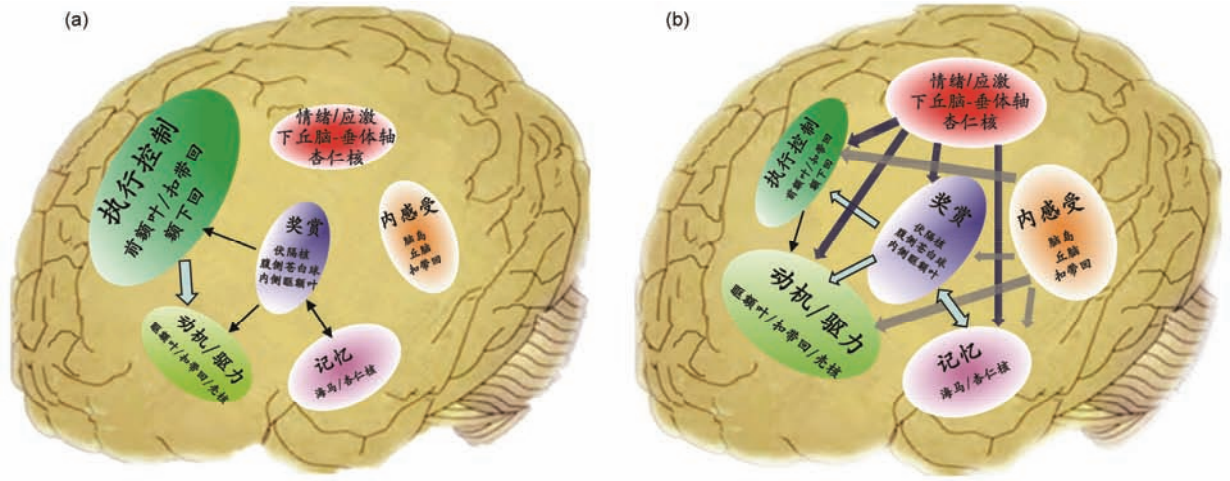

图 1 (网络版彩色)正常(a)与成瘾(b)的神经环路交互模式示意图. (a) 当这些神经环路以一种平衡的方式整合来自个体内外部的信息时, 个体会做出合适的抑制与决策等行为; (b) 当成瘾个体在对药物相关刺激进行加工时, 奖赏、动机及记忆环路会挣脱执行控制环路对其的调节, 同时内感受环路与情绪环路也会进一步削弱执行控制环路对奖赏等环路的控制作用, 从而致使个体选择继续用药

Figure 1 (Color online) The interactive neural circuitry model of addiction. (a) Shows how the relevant brain circuits interact with one another to attain proper inhibitory control and hence good decision making; (b) shows how the enhanced activities of six circuits (i.e., reward, motivation, memory, executive control, mood, and interoception)overwhelm the PFC's inhibitory control and hence lead to craving

6.1 采用先进研究技术, 推动多技术融合

如前所述, 技术的革新推动了研究的向前发展. 现阶段, 已有很多脑影像技术(如EEG, fMRI, fNIRS等)和脑刺激技术(如TMS(Transcranial Magnetic Stimulation)和tDCS (transcranial Direct Current Stimulation))可用于认知神经研究中, 从神经元激活的电场、磁场、代谢物等不同的角度来测量或者操控局部脑区的活动. 然而, 目前的成瘾研究领域基本上只采用一种测量技术, 缺乏优势整合. 这些技术都有各自的优势与局限, 只有将这些技术结合起来, 才能有效克服各种方法的局限性, 最大限度地发挥各种方法的优势. 比如, fMRI技术在空间分辨率上可以达到毫米级别, 但其受生理机制的限制, 时间分辨率比较低, 一般为数秒, 较难实现实时反映刺激后大脑内部血氧含量变化的时间进程; 而EEG作为一种无创记录大脑活动电生理信号的方式, 具有很高的时间分辨率(毫秒级), 具有揭示认知加工的时间进程的优势, 但空间分辨率较低. 已有一些研究者开始尝试结合这两种研究技术的优点, 推动我们对成瘾者背后认知和神经基础的理解[111]. 最终, 希望后续的研究能结合更多研究技术的优势, 进行多技术的融合研究, 这样的研究将有助于加深我们对成瘾者内在认知神经基础的多层面了解.

6.2 关注共病问题, 尝试弄清成瘾与其他精神疾病的关系

物质成瘾常常伴随有诸如焦虑、抑郁等之类的精神疾病, 甚至与其他成瘾问题之间具有共病关系. 目前的研究主要都倾向于报告这些共病, 但是并没有将这些共病作为一个变量进行分析, 没有理清这些共病问题在成瘾的发生、发展、戒断与复吸过程中起着怎样的作用; 因此, 搞清楚共病关系将有助于我们对病人成瘾类型进行细分以及更深入理解其背后的认知和神经基础, 从而找到更有针对性的治疗和干预措施.

6.3 构建和完善生物标记, 形成行为和脑相结合的诊断系统

目前对成瘾的诊断主要还是基于行为的询问, 而不是基于脑成像以及生物分子等技术手段. 未来的研究应该将脑成像等技术更多地运用于成瘾病灶的诊断和定位中去, 实现精准医疗的目的. 例如: 药物成瘾与腹侧前额叶的功能减退有关, 脑成像技术运用有助于诊断病人该神经回路的变化情况, 从而更精确地诊断病情发展情况. 相似地, 长期物质滥用可以导致个体的纹状体内多巴胺D2受体不足, 而正电子发射型计算机断层显像技术(positron emission

tomography, PET)技术可以有效地定位与检测纹状体中的多巴胺D2受体数量，为精准诊断与预测病情提供了可能.

6.4 开发基于脑神经回路的干预方法，建立从行为到脑刺激相结合的干预措施

目前对成瘾病人的干预多是基于认知行为疗法，尽管这种行为方法被广大研究者所接受，但其疗效并不十分令人满意，成功戒断康复的病人的复吸率仍然居高不下. 未来的方向应该致力于开发基于成瘾脑回路的干预手段，结合行为疗法与脑刺激，从而快速有效地减轻病人症状，帮助其走出吸毒-戒断-康复-复吸的死循环. 例如，近期有研究发现，通过经颅磁刺激技术(rTMS)刺激平均十多年吸毒史的海洛因成瘾者的左侧背外侧前额叶，可以成功降低患者机体对药物的渴求度[112]，表明通过无创性磁刺激可以增强个体执行功能，从而减轻症状，达到快速治疗的目的. 因此，未来的研究应努力探索并建立一套行为-脑-药物相结合的干预体系，从而为成瘾病人的干预与治疗提供实质性的帮助.

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Cognitive dysfunction and underlying neural basis in substance addiction

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As one of the most serious public health problems that extract a high toll on individuals and the society as a whole, substance abuse/addiction has attracted much attention from both researchers and the public. According to the DSM-5, substance addiction is a chronically relapsing psychiatric disorder that has been characterized by compulsion to seek and use drugs, loss of control in limiting intake despite serious negative consequences. However, more than 80% of the individuals with addiction fail to seek treatment, perhaps reflecting their cognitive function impairments. Previous studies have showed that most drugs of abuse exert their reinforcing effects and produce euphoria by inducing dopamine surges in limbic regions, which then have cascading effects on other neurotransmitter systems, leading to characteristic plastic adaptions; significant changes in neural circuits implicated in reward, attention, inhibitory control, decision making and interoception; and cognitive dysfunctions. However, much is still to be learned about the neural mechanisms involved in drugs' effects on cognitive functions and the vicious cycle of "drug abuse – withdrawal – recovery – relapse". For a better understanding of the causes of substance addiction and its underlying neural mechanisms, we provide an integrative review of behavioral and neuroimaging studies in substance addiction, introduce a neurobiological model of substance addiction, and finally propose future directions for research and clinical treatment.

First, we summarize the research on the cognitive and neural mechanisms involved in substance addiction. (1) Drug-related cues can enhance the activities in the mesocorticolimbic system implicated in reward and drug motivation, which then result in increased attention to the drug-related stimuli. Thus, the neural changes in the frontolimbic system may be a potential neural basis for attentional bias toward drugs in individuals with addiction. (2) The deficit in inhibitory control typically observed in individuals with substance addiction may be due to a dysfunction in their prefrontal cortex-striatothalamic circuitry. (3) These individuals' poor decision making may be a product of an imbalance between three separate, but interacting, neural systems: the amygdala-striatum (an impulsive system); the prefrontal cortex (a reflective system); and the insula (the interoceptive system). (4) Emerging evidence shows that individuals with drug addiction have interoceptive processing deficits, perhaps due to dysfunctions in brain systems such as the insula and the anterior cingulate cortex.

Second, we introduce a neurobiological model of substance addiction that depicts addiction as a result of an imbalance of six interactive circuits (i.e., reward, motivation/drive, memory, executive control, mood, and interoception). These brain circuits interact with one another to attain proper inhibitory control and hence good decision making. During addiction, however, the enhanced activities of six circuits (i.e., reward, motivation, memory, executive control, mood, and interoception) overwhelm the PFC's inhibitory control and hence lead to craving.

Finally, we propose that future studies should (1) use multi-modal imaging techniques, (2) pay attention to comorbidity and clarify the association between addiction and other psychiatric disorders, (3) discover more biomarkers and optimize the diagnostic system using both behavioral and neuroimaging information, and (4) develop brain-based intervention techniques. Such studies should deepen our understanding of substance addiction and provide insights to its treatment.

substance addiction, attention, inhibitory control, decision-making, interoception

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