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·研究构想(Conceptual Framework)·

冲动性对不同成瘾行为发展的调控及其神经机制*

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摘 要 近年来越来越多的研究证据提示, 个体冲动性在成瘾疾患发生发展机制中具有关键作用, 可能成为成瘾行为的潜在易感标记以及早期识别和干预的重要靶点, 但冲动性对不同成瘾行为变化发展的调控机制尚不明确。项目拟综合跨成瘾谱系比较、纵向追踪设计、冲动行为干预等研究途径, 采用人格测量、神经认知、神经影像等技术, 首先比较尼古丁依赖者与网络游戏成瘾者的冲动性结构及其在前额叶–纹状体环路的结构功能改变; 然后采用混合分组设计筛选出具有高低冲动性的非成瘾青少年进行连续追踪研究, 考察冲动性对尼古丁依赖与网络游戏成瘾的预测效力; 并采用认知行为训练, 对吸烟成瘾者与网络游戏成瘾者进行冲动干预, 考察行为干预对冲动性水平及前额叶–纹状体环路功能的改变, 以及对不同成瘾行为发展的抑制后效。旨在探索冲动性作为成瘾的潜在易感标记及干预靶点的效力。

关键词 成瘾疾患; 冲动性; 抑制控制; 尼古丁依赖; 网络游戏成瘾

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1 研究背景及意义

物质使用与成瘾障碍(Substance Use & Addictive Disorders)已成为严重的社会公共卫生问题。据世界卫生组织报告, 2010 年全世界大约有 1600~3800 万人存在药物依赖或成瘾问题。在我国, 2014 年登记在册的吸毒成瘾人员数量已达 258 万。酒精依赖与吸烟问题更是世界各国面临的严峻考验。根据一项大型流行病学调查, 我国普通人群的饮酒率为 59%、酒精依赖者比例约为 3.8% (伍志刚, 苏中华, 郝伟, 2004); 卫生部统计, 2006 年我国约有 3.5 亿吸烟者, 占整人口比例 25%以上。与物质滥用类似, 赌博也是世界各国普遍存在的社会问题。大约有 80%~90%的成年人都参与过赌博活动, 赌博成瘾的终生流行率约为 1%~2%, 在东方文化国家中约为 2.5%~4.0% (Loo, Raylu, & Oei, 2008)。此外, 近年来青少年网络成瘾问题成为又一个世界瞩目的社会与健康问题, 尤其是在亚洲的一些国家和地区(Ko, Yen, Yen, Chen, & Chen, 2012)。网络游戏成瘾或网络游戏障碍(Internet gaming disorder)已被 DSM-5 正式纳入研究手册(Petry et al., 2014)。严重的成瘾行为一旦形成, 除了某些可以采用药物替代治疗外, 目前尚无确切的治疗方法。因而, 成瘾的早期识别和干预是其防治的关键, 特别是在成瘾行为发展至严重成瘾障碍之前的早期阶段, 有效识别具有较高易感水平和成瘾倾向的重点人群, 采用行为或药物干预有可能阻止成瘾行为进一步发展。探索成瘾的神经认知标记(Neurocognitive Marker), 深入揭示成瘾易感性的神经生物机制, 可以为识别成瘾早期干预的靶点、预警具有成瘾高风险的重点人群提供可能途径, 对成瘾的防治具有重要意义。

在成瘾行为的形成过程中, 物质(药物)成瘾由于同时受到个体易感素质和药物生化作用的双重干扰, 其成瘾个体的神经认知异常表现(如高冲动、行为抑制能力减退、神经系统功能下降等)在

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性质上难以解释：这些异常是个体本身的先天易感特质，还是药物对大脑结构功能慢性损伤的结果(Dalley, Everitt, & Robbins, 2011)？而非物质成瘾行为由于不涉及物质或药物的作用，有效排除了药物效应的干扰，为研究成瘾的原始易感机制提供了理想的模型(Clark & Limbrick-Oldfield, 2013; Holden, 2010; Leeman & Potenza, 2012; Potenza, 2008)，比较物质成瘾与非物质成瘾形成发展过程有助于深入揭示成瘾的神经生物机制。一般认为，与成瘾相关的神经认知易感因素(Predisposing Factors)将同时在物质成瘾人群与非物质成瘾人群中表现，而与长期滥用药物相关的损伤效应将只出现在物质成瘾人群中而不会出现在非物质成瘾人群中(Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009a, 2009b; Verdejo-García, Lawrence, & Clark, 2008)，通过研究识别物质成瘾者与非物质成瘾者的共同神经认知异常及其神经生物基础，对于探索成瘾的神经认知标记具有重要作用。

近年来成瘾领域越来越多的汇聚证据提示，冲动性(Impulsivity)可能是与成瘾行为密切相关的潜在神经认知标记(de Wit, 2009; Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010; Ersche et al., 2012, 2013; Moffitt et al., 2011; Verdejo-García et al., 2008; Volkow & Baler, 2012)。研究发现，药物成瘾者与其未使用过药物的健康同胞兄弟姐妹有类似的高冲动特质，并且他们的反应抑制功能都要显著差于正常对照组(Ersche et al., 2010, 2012)；儿童和青少年时期的高冲动或抑制能力不足可以预测药物滥用问题的开始及成年后药物滥用的严重程度(Audrain-McGovern et al., 2009; Nigg et al., 2006; Tarter et al., 2003)，青少年时的高冲动还可以预测成年后的赌博问题(Lee, Storr, Ialongo, & Martins, 2011; Slutske, Moffitt, Poulton, & Caspi, 2012)；此外，药物成瘾者与赌博成瘾者在特质冲动、反应抑制、冲动决策等方面同时表现出类似的高冲动性或抑制能力损伤(Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Lawrence et al., 2009a, 2009b; Yan et al., 2014)。

然而，尽管冲动性可能成为成瘾的一种重要神经认知标记(Jentsch & Taylor, 1999; Robbins, Gillan, Smith, de Wit, & Ersche, 2012)，但是目前这一观点仍然没有定论(Dalley et al., 2011; de Wit, 2009)，主要是由于缺少足够的遗传学、纵向追踪/前瞻设计、跨成瘾谱系比较等方面的研究证据，尤其是当前已有结果大多是建立在成瘾性药物的研究基础上，较为缺乏非物质成瘾行为的聚合证据以及成瘾谱系的对比研究结果。另外，由于冲动性是一种具有多维特征(Multifaceted)的神经认知结构(Dalley et al., 2011; Evenden, 1999; Pattij & De Vries, 2013)，不同的人格评估(如 Barratt Impulsiveness Scale, BIS)、行为测试(如 Stop-Signal Task)等方法所测的冲动性结构并不统一，哪些冲动性结构在成瘾的发生发展中起决定性作用并不清楚。

综上所述，本项目拟结合跨成瘾谱系比较和纵向设计范式，研究冲动性在物质成瘾和非物质成瘾形成发展中的调控作用及神经生物机制，探索冲动性及其神经系统的结构功能变化与不同成瘾行为的发动、维持到强迫性转换的关系，可以提供新的视角来回答冲动性是否能作为成瘾的神经认知标记这一重要科学问题，并为不同类型成瘾行为的识别和早期干预提供依据

2 国内外研究现状

2.1 成瘾障碍及其形成机制

一般认为，药物成瘾(Drug Addiction)是一种以强迫性寻求和使用药物、对用药失去控制能力为主要特征的慢性复发性脑疾病(Goldstein & Volkow, 2002; Leshner, 1997)。药物成瘾的主要形成途径是：在偶然环境诱因或个体易感素质的启动下，个体反复接触和使用药物，药物的化学成分直接作用于大脑，广泛改变大脑神经系统的结构和功能，并进一步推动觅药和用药行为，最终导致严重的成瘾障碍的发生。而某些纯粹的行为活动(如赌博)尽管不涉及外源性药物的神经毒理作用，但在个体易感素质的催化下反复从事，经由外部行为刺激而引起大脑内部生理状态失衡，也会导致成瘾状态的出现。在成瘾障碍形成的脑机制方面，成瘾的双系统理论认为，成瘾是大脑反思系统(Reflective System)和冲动系统(Impulsive System)之间失衡的结果(Bechara, 2005; Deutsch & Strack, 2006; Stacy & Wiers, 2010)。冲动系统的神经基础主要是杏仁核–纹状体系统，它在自然奖赏和药物奖赏的情绪及动机效应中起关键作用，是一个相对内隐的、无意识的、自动化的系统；反思系统的神经基础主要是前额叶皮质系统，包括

背外侧前额叶、腹内侧前额叶(含眶额叶)、前扣带回、额下回等脑区，它在冲动控制、计划决策、情绪调节等过程中起重要作用，是相对外显的、有意识的、受控性的系统。当以前额叶为中心的反思系统控制能力下降、以纹状体为中心的冲动系统功能亢进时，个体的行为变得冲动而不可控。双系统理论得到了大量成瘾相关的额叶–纹状体环路功能异常(Fronto-Striatal Dysfunction)证据的进一步支持(Balodis et al., 2012; Courtney, Ghahremani, & Ray, 2013; Ersche et al., 2011, 2012, 2013; Kalivas, Volkow, & Seamans, 2005; Limbrick-Oldfield, van Holst, & Clark, 2013)。然而，一个有待回答的问题是：到底是纹状体系统的“高冲动”，还是前额叶系统的“低控制”，又或是两者的叠加，是个体反复持续地从事成瘾行为、最终导致严重成瘾障碍形成的易感基础？

2.2　冲动性的表现形式、测量方法及神经基础

冲动性(Impulsivity)是一种多维度的神经心理结构，其简单定义是“不加深思熟虑就过早行动的一种行为倾向” (Dalley et al., 2011; Evenden, 1999; Pattij & De Vries, 2013; Verdejo-García et al., 2008)。其表现形式或成分主要包括：一是奖赏预期敏感性(Sensitivity to Reward Anticipation)，即对预期可得的奖赏具有较高的敏感度；二是去抑制(Disinhibition)或反应控制不足(Response Dyscontrol)，即无法及时有效地制止已经启动的行为；三是计划性低下(Poor Planning)，即行动缺乏谋划、不做长远打算(Dalley et al., 2011; Robbins et al., 2012)。冲动性的测量方式主要有人格量表和实验室任务：前者如 Barratt 冲动量表(Barratt Impulsivity Scale, BIS-11, Patton, Stanford, & Barratt, 1995)、UPPS-P 冲动行为量表(UPPS-P Impulsive Behavior Scale, Whiteside & Lynam, 2003)等，BIS-11 包含有 30 个项目，可以测得一个冲动性总分及三个因素分数，即注意(Attentional)、运动(Motor)以及无计划(Non-planning)冲动性；UPPS-P 包含 59 个项目，测量 5 个因素，即积极紧急性(Positive Urgency)、消极紧急性(Negative Urgency)、缺乏计划(Lack of Premeditation)、缺乏耐心(Lack of Perseverance)及感觉寻求(Sensation-Seeking)。测量冲动性的实验室任务主要包括延迟折扣任务(Delay Discounting Task, DDT, Kirby, Petry, & Bickel, 1999; Kirby & Petry, 2004)、反应抑制任务(Stop-Signal Task, Logan, Schachar, & Tannock, 1997; Stroop Task, Macleod, 1991)等，DDT 主要考察对即时奖赏(预期)的敏感性，Stop-Signal 和 Stroop 任务主要考察抑制控制功能。此外，还有一些较复杂的神经认知任务，如爱荷华赌博任务(Iowa Gambling Task, IGT, Bechara, Tranel, & Damasio, 2000)、剑桥赌博任务(Cambridge Gamble Task, CGT, Rogers et al., 1999)等，可用于考察风险决策时的冲动性选择。

但从神经解剖学(Neuroanatomy)的角度看，冲动性的结构大体可分为三类：一是特质冲动(Trait Impulsivity，如 BIS-11 所测得的冲动性人格)，与腹侧纹状体(Ventral Striatum, VS)/伏隔核(Nucleus Accumbens, NAc)的功能紧密相关，高 BIS-11 得分与纹状体多巴胺功能下降有关，NAc D2/3 受体密度减少可预测高特质冲动(Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley et al., 2007; Ersche et al., 2010; Lee et al., 2009)；二是等待冲动(Waiting Impulsivity，如 DDT 所测得的延迟奖赏折扣)，与腹内侧前额叶到腹侧纹状体的神经环路(vm-PFC—NAc/VS)功能有关；三是停止冲动(Stopping Impulsivity，如 Stop-Signal 任务所测得的反应抑制)，与腹外侧前额叶(含额下回，IFG)/前扣带回到背侧纹状体(尾状核、壳核)的神经环路(vl-PFC/ACC—Caudate Nucleus & Putamen)密切相关(Dalley et al., 2011; Robbins et al., 2012)。目前研究者大多认同冲动性在成瘾中起重要作用，但由于其成分及神经结构非常复杂，冲动性在成瘾发生发展中的微观机制并不明确。

2.3　物质成瘾人群的高冲动性及对其的解释

高冲动性是自我控制低下的重要表现形式，也被认为是成瘾的核心标志之一(O’Brien, Volkow, & Li, 2006)。许多研究发现，不同的物质成瘾群体，包括兴奋剂(如可卡因、苯丙胺类)、阿片类(如海洛因、吗啡)、酒精等物质滥用者，均表现出一致的高冲动性特征(Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Dick et al., 2010; Perry & Carroll, 2008; Potenza & Taylor, 2009; Verdejo-García et al., 2008)。比如，在特质冲动上(由类似 BIS 的自陈人格量表评估)，可卡因依赖者(Coffey, Gudleski, Saladin, & Brady, 2003; Moeller et al., 2004)、MDMA 滥用者(Butler & Montgomery, 2004; Parrott, Sisk, & Turner, 2000)、混合兴奋剂依

赖者(Ersche et al., 2010, 2012; Leland & Paulus, 2005)、酒精依赖者(Bjork, Hommer, Grant, & Danube, 2004; Mitchell, Fields, D'Esposito, & Boettiger, 2005; Whiteside & Lynam, 2003)、海洛因滥用者(Kirby et al., 1999; Madden, Petry, Badger, & Bickel, 1997)均表现较高的冲动性特质。在停止冲动(由 Stop-Signal、Go/No Go、Stroop 等反应抑制任务所评估)方面，可卡因滥用和依赖者(Albein-Urios et al., 2012; Fillmore & Rush, 2002; Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003; Li, Milivojevic, Kemp, Hong, & Sinha, 2006; Verdejo-García, Rivas-Pérez, Vilar-López, & Pérez-García, 2007)比正常对照组需要更长的时间来抑制反应且犯了更多的误按错误，类似的结果被发现广泛存在于酒精依赖(Goudriaan, Oosterlaan, De Beurs, & van Den Brink, 2006; Kamarajan et al., 2005; Kaufman et al., 2003; Lawrence et al., 2009a, 2009b; Noël, Bechara, Dan, Hanak, & Verbanck, 2007)、苯丙胺类滥用(Monterosso, Aron, Cordova, Xu, & London, 2005; Salo et al., 2002; Simon et al., 2000)等人群中，还有少量研究发现海洛因(Ersche, Clark, London, Robbins, & Sahakian, 2006; Verdejo-García & Perez-García, 2007)及尼古丁(Krishnan-Sarin et al., 2006; Spinella, 2002)依赖人群也有类似的表现。在等待冲动(主要由 DDT 延迟折扣任务所测得)方面，多数研究表明兴奋剂类物质依赖者(Heil, Johnson, Higgins, & Bickel, 2006; Hoffman et al., 2006, 2008; Kirby & Petry, 2004; Coffey et al., 2003; Monterosso et al., 2007)、阿片类物质滥用者(Cheng, Lu, Han, González-Vallejo, & Sui, 2012; Kirby et al., 1999; Kirby & Petry, 2004; Madden et al., 1997)、酒精成瘾者(Bobova, Finn, Rickert, & Lucas, 2009; Field, Christiansen, Cole, & Goudie, 2007; MacKillop et al., 2010; Mitchell et al., 2005; Mitchell, Tavares, Fields, D'Esposito, & Boettiger, 2007)、尼古丁依赖者(Bradford, 2010; Fields, Leraas, Collins, & Reynolds, 2009; Heyman & Gibb, 2006; Jones, Landes, Yi, & Bickel, 2009; Kirby & Petry, 2004; Reynolds et al., 2007; Reynolds, Leraas, Collins, & Melanko, 2009; Sweitzer, Donny, Dierker, Flory, & Manuck, 2008)等人群对延迟奖赏的折扣程度要显著高于正常对照组。尽管在物质成瘾人群高冲动性方面也有一些阴性结果(参见 Albein-Urios et al., 2012; Fishbein et al., 2007; MacKillop et al., 2011)，但大多数研究表明高冲动性是物质成瘾人群的重要特征。对于物质成瘾人群高冲动性的解释可能有两种：其一，长期的药物滥用导致成瘾人群行为变得更加冲动，这与慢性使用药物的神经生物效应有关(比如前额叶皮层的细胞死亡、组织萎缩，纹状体部位的白质、灰质密度改变等大脑结构变化)，得到了来自前临床动物实验及人类神经影像学的大量证据支持(de Wit, 2009; Ersche et al., 2011, 2012, 2013; Everitt & Robbins, 2005; Goldstein & Volkow, 2002; Goldstein et al., 2007; Limbrick-Oldfield et al., 2013; Robbins, Ersche, & Everitt, 2008; Schoenbaum & Shaham, 2008; Volkow et al., 2001; Winstanley, Olausson, Taylor, & Jentsch, 2010)。其二，高冲动性是个体成瘾前就已存在的特征，作为药物成瘾的一种易感标记，推动个体从娱乐性使用药物到强迫性使用药物的转变，并在戒断后复吸的过程中施加重要影响(Belin et al., 2008; Dalley et al., 2011; de Wit, 2009; Ersche et al., 2010; Pattij & De Vries, 2013; Robbins et al., 2012; Tarter et al., 2003; Verdejo-García et al., 2008)。但这两种解释并不必然是互斥的：药物使用者可能发病前就具有高冲动特质，而这种高冲动性会随着慢性药物使用进一步加剧(Verdejo-García et al., 2008)。为寻求可用于成瘾早期识别和干预的靶点，研究者更青睐采取精巧严密的设计来证实冲动性是否能够作为成瘾的潜在易感标记。

2.4 冲动性作为成瘾的潜在易感标记

目前探索冲动性作为成瘾的潜在易感标记的人类研究主要有三种途径：1)遗传学研究; 2)纵向追踪设计; 3)跨成瘾谱系比较。在遗传学研究方面，研究试图找到药物成瘾者及其同卵/异卵双生子或一级亲属(如父母、同胞兄弟姐妹)之间同时存在高冲动及相关生物学证据。早期的一些研究发现，人格层面的特质冲动性、新颖寻求(Novelty Seeking)与药物成瘾行为有关且与多巴胺受体基因 DRD4 存在一定程度的关联(Agrawal, Jacobson, Prescott, & Kendler, 2004; Kreek, Nielsen, Butelman, & LaForge, 2005)。近期有研究大样本分析了药物成瘾者及其从未使用过成瘾物质的同胞兄弟姐妹(Siblings)的 BIS 特质冲动及 Stop-Signal 反应抑制，发现与正常对照组相比，药物成瘾者和其同胞兄

弟姐妹具有更高水平特质冲动以及更差的反应抑制能力(Ersche et al., 2010, 2012, 2013), 且在前额叶–纹状体通路(Fronto-Striatal)存在一些结构异常, 包括右侧额下回(Inferior Frontal Gyrus, IFG)白质密度减少、壳核(Putamen)灰质容量增大等(Ersche et al., 2012)。这些重要发现提示, 冲动性可能成为药物成瘾的一种易感标记或内表型(Everitt & Robbins, 2013; Robbins et al., 2012; Volkow & Baler, 2012)。一些纵向追踪研究也发现了冲动性在预测成瘾行为发展中的作用。研究显示, 青少年时期的冲动性决策可以预测首次吸烟行为、冲动抑制能力不足可以预测药物滥用问题和酗酒的严重程度 (Audrain-McGovern et al., 2009; Goudriaan, Grekin, & Sher, 2011; Nigg et al., 2006; Wong et al., 2006), 儿童和青少年时期的高冲动还可以预测成年后的赌博问题(Lee et al., 2011; Slutske et al., 2012; Vitaro, Arseneault, & Tremblay, 1997), 但这些结果存在着一些挑战, 如成长环境和家族发病史等因素的影响(Verdejo-García et al., 2008)。近年来有少量研究借助非物质成瘾行为, 与药物成瘾进行跨成瘾谱系的比较研究, 试图将成瘾的易感因素与药物相关的效应进行分离。研究发现, 赌博成瘾者与酒精依赖者(Lawrence et al., 2009a, 2009b)、可卡因依赖者(Albein-Urios et al., 2012)具有类似的反应抑制功能下降且 BIS 得分都高于正常对照组, 赌博成瘾者与海洛因成瘾者具有类似的冲动性决策(Yan et al., 2014)。还有一些研究发现, 网络成瘾人群也表现出较高的特质冲动和较差的抑制功能(Cao, Su, Liu, & Gao, 2007; Choi et al., 2014; Dong, DeVito, Du, & Cui, 2012; Lee et al., 2012), 并且在一些与冲动性密切相关的行为反应(如奖赏寻求、认知控制等)及相关的神经环路功能上表现出与药物成瘾相类似的特点(李琦, 齐玥, 田莫千, 张侃, 刘勋, 2015), 不过, 目前还不多见网络成瘾与药物成瘾进行严格对照的比较研究。

以上研究结果提示, 冲动性可能是成瘾行为的易感基础。但值得注意的是, 人类实验在条件控制上存在许多困难, 研究很难保证除冲动性变量之外其他条件的同质性, 一些混淆变量如成长环境的差异、共患精神或心理疾病、生活应激水平等因素, 可能对研究结果产生不利影响。结合不同的研究途径、采取更加严密的设计, 将有助于进一步探索冲动性作为不同成瘾行为潜在易感标记的效力。

2.5　干预冲动性对成瘾行为变化发展的影响

成瘾疾患目前尚无确切疗法, 早期识别和干预是其防治的关键, 研究者们试图寻找到可供行为或药物干预的准确靶点, 以阻止成瘾行为进一步发展。从成瘾的发生发展机制来看, 成瘾的表现似乎是从早期的冲动机制逐渐向后期的强迫机制转移(Belin et al., 2008; Dalley et al., 2011; Everitt et al., 2008; Robbins et al., 2012), 因此对个体冲动性进行干预或许能够阻止成瘾行为继续发展。研究发现, 采用认知行为训练能够降低兴奋剂成瘾者的冲动性选择(延迟奖赏折扣), 并部分改善了成瘾的状况(Bickel, Yi, Landes, Hill, & Baxter, 2011; Wesley & Bickel, 2014; Wexler, 2011), 类似的结果在阿片类成瘾者中得到重复(Landes, Christensen, & Bickel, 2012); 冲动行为抑制训练还能促进酒精依赖者的临床治疗效果及对酒精的认知偏差(Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011)。一些临床药物治疗也能在一定程度上抑制成瘾行为, 如治疗多动症(ADHD)的药物盐酸阿托莫西汀(Atomoxetine)能够降低患者的冲动性同时减少严重酒精滥用的情况(Bari et al., 2011; Chamberlain, Müller, Robbins, & Sahakian, 2006; Wilens et al., 2008; Wilens & Morrison, 2011), 前临床实验也发现, 盐酸阿托莫西汀能够降低实验动物对海洛因和可卡因的觅药冲动, 以及减少戒断后的复吸情况(Economidou, Dalley, & Everitt, 2011; Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009; Robinson et al., 2008)。这些研究结果提示, 冲动性可能成为抑制成瘾发展的重要干预靶点(Pattij & De Vries, 2013)。然而, 目前相关的研究数量较为有限, 同时也还也存在一些阴性结果(Levin et al., 2009; McRae-Clark et al., 2010; Walsh et al., 2013), 因而干预个体的冲动性对成瘾行为变化发展的抑制后效尚需进一步探索和验证。

3　研究问题及切入点

如前所述, 冲动性可能成为成瘾障碍的易感神经认知标记或内表型, 是成瘾障碍早期识别和干预(行为训练或药物治疗)的潜在靶点, 但由于目前研究的一些局限和不足, 该假设还有待于进一步的实验证据予以证实。本项目拟解决的关键科学问题主要包括：1)冲动性的不同结构/维度在

物质成瘾与非物质成瘾中的异同变化特征，冲动性结构能否作为跨成瘾行为谱系的易感标记及其可能的神经生物学基础；2)冲动性在预测不同成瘾行为发展过程中的作用及其机制，干预冲动性对成瘾行为发展的抑制效力及潜在的神经功能重塑机制。我们拟结合跨成瘾谱系比较研究(物质成瘾 vs 非物质成瘾)、纵向追踪设计途径，采用人格测量、神经认知、神经影像等技术，进一步探索冲动性对成瘾行为的调控及其神经生物机制。在成瘾谱系的选择上，本项目主要关注尼古丁依赖与网络游戏成瘾，其主要考虑是：第一，我们的前期相关研究已经通过海洛因成瘾与赌博成瘾的直接对比，获得了一些初步的行为学与影像学结果(Yan et al., 2014)，为了汇聚更多的跨成瘾谱系比较研究的证据，本课题选择了以吸烟成瘾替代海洛因成瘾、网络游戏成瘾替代赌博成瘾，继续推进物质成瘾与非物质成瘾的比较研究。第二，一些研究表明，青少年尼古丁使用与网络成瘾具有密切的关系(Dalbudak et al., 2013)，两者之间往往存在共病现象或互为风险因素(Fisoun, Floros, Siomos, Geroukalis, & Navridis, 2012; Ko et al., 2013; Lee, Han, Kim, & Renshaw, 2013)，因此有必要深入对比分析冲动性在尼古丁依赖与网络游戏成瘾发生发展中的共同作用及其机制。第三，尼古丁使用、网络游戏使用作为世界各国普遍并不违法的成瘾行为，在青少年群体具有广泛的易得性和代表性，研究冲动性对尼古丁依赖与网络游戏成瘾的调控机制及其作为干预靶点的效力，具有重要的理论意义和应用价值。本项目主要内容：其一，比较吸烟成瘾者与网络游戏成瘾者的特质冲动、等待冲动、停止冲动及其前额叶–纹状体环路的结构功能改变，以验证冲动性作为跨成瘾谱系的易感标记以及相应的生物基础；其二，筛选具有高、低冲动水平的非成瘾个体，通过匹配控制混淆变量，连续追踪 2~3 年，观察各组吸烟成瘾与网络游戏成瘾的发生几率，考察冲动性对跨谱系成瘾行为的预测效力，进一步验证冲动性作为成瘾行为的潜在易感素质；最后，采用认知行为干预方法，对吸烟成瘾者与网络游戏成瘾者进行冲动抑制训练，比较实验前后各组的冲动性水平、前额叶–纹状体环路功能的变化情况，并观察实验后 1~24 个月的成瘾行为变化状况，以考察冲动性作为成瘾行为潜在干预靶点的有效性。

4 研究构想

4.1 研究 1 尼古丁依赖者和网络游戏成瘾者的冲动性及其神经基础

本研究旨在通过跨成瘾谱系比较设计，探索物质成瘾与非物质成瘾中的冲动性结构及其神经生物基础。在青年大学生群体中进行大规模抽样，选取 50~80 名吸烟成瘾者、50~80 名网络游戏成瘾者以及 50~80 名在性别、年龄、教育年限等方面严格匹配的控制组被试。入组标准：吸烟成瘾者符合 DSM-IV 尼古丁依赖的诊断标准(Structured Clinical Interview for DSM-IV disorders, SCID, First, Spitzer, Gibbon, & Williams, 1995)，并满足在尼古丁依赖筛选量表(Fagerstrom Test for Nicotine Dependence, FTND, Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991)上的得分≥4，排除其他物质成瘾及网络游戏成瘾；网络游戏成瘾者符合目前主流网络成瘾的诊断筛选标准(Young's Internet Addition Test, IAT, Young, 1998, 2009)，并符合 DSM-5 建议的网络游戏成瘾诊断标准(Petry & O'Brien, 2013; Tao et al., 2010)，排除吸烟成瘾及其他物质成瘾。控制组被试与前两组严格匹配，无吸烟成瘾或网络游戏成瘾问题。排除标准：所有被试视力或矫正视力正常、均无酒精滥用或依赖情况、无非法药物滥用(如海洛因、可卡因、冰毒、摇头丸、麻古等)、无脑外伤、神经疾病或精神疾病史、参与实验前一周内未用影响神经功能的医学药物。使用抑郁自评量表(SDS)、焦虑自评量表(SAS)、临床心理症状清单(SCL-90)等评估所有被试的基本情绪及心理症状状况，适当控制或排除情绪问题对实验任务操作绩效的干扰。

冲动性评估方法：1)使用 Barratt 冲动性量表(BIS)、UPPS-P 冲动行为量表测试被试的特质冲动(Trait Impulsivity); 2)采用延迟折扣任务(DDT)、基于奖赏的冲动性决策任务(IGT)测试被试的等待冲动(Waiting Impulsivity); 3)使用反应抑制任务(Stop-Signal Task)和干扰抑制任务(Stroop Task)测试被试的停止冲动(Stopping Impulsivity)。除量表外所有任务都在计算机上实施。

神经影像学测试：1)使用 3T Philips Trio MRI 设备采集各被试组(20~30 人)的结构像，采用基于纤维束示踪的空间统计(Tract-Based Spatial Statistics, TBSS)方法比较各组的白质纤维束密度(衡量指标

Fractional Anisotropy, FA)，并重点分析各组在感兴趣区(Region of Interest, ROI)的差异，ROI 的选择参照已有研究中不同冲动结构对应的脑区，即腹内侧前额叶、前扣带回、额下回、伏隔核、尾状核–壳核；采用基于体素的形态学分析(Voxel-Based Morphometry, VBM)方法比较各组的大脑灰质密度差异。2)采用事件相关的 fMRI 实验设计，在被试反应抑制任务(Go/No Go)与冲动性决策任务(IGT)的同时，进行磁共振成像扫描，分析各组在感兴趣区的激活程度差异(ROI 包括 vmPFC, dlPFC, dACC 等), fMRI 实验程序参见相关的任务范式及项目组已建立的 fMRI 实验任务范式。

4.2　研究 2 冲动性对尼古丁依赖和网络游戏成瘾行为发展的纵向预测

采用纵向追踪设计有助于研究冲动性在预测成瘾行为发展中的作用，先前研究显示，青少年时期的冲动性可以在一定程度上预测不同的成瘾行为变化，但一些外部混淆因素对其结果造成较大干扰。本研究拟对处于相似外部环境的一般青少年群体进行连续追踪，考察冲动性对跨谱系成瘾行为发展的预测效力，进一步验证冲动性作为成瘾行为的潜在易感素质的可能性。采集处于青少年期的中学生、大学生样本，进行大规模抽样测试，分别筛选具有高冲动、低冲动特征的非成瘾被试各 100~200 名，进行连续 2~3 年的追踪研究，调查两组人群在尼古丁依赖与网络游戏成瘾等方面的变化趋势，将家庭经济地位、生活事件应激等心理社会变量作为协变量予以控制，分析冲动性对成瘾行为发展的预测。

采用混合设计方法，综合评定高、低冲动性水平分组，以特质冲动和停止冲动作为主要维度，采用 2(高特质冲动、低特质冲动)×2(高停止冲动、低停止冲动)设计分为 4 组，即组 1 高特质冲动–高停止冲动，组 2 高特质冲动–低停止冲动，组 3 低特质冲动–高停止冲动，组 4 低特质冲动–低停止冲动。特质冲动使用 Barratt 冲动性量表(BIS)进行评估，高特质冲动的界定标准：BIS 总分大于总样本平均分加上一个标准差(*M*+*SD*)；低特质冲动的界定标准：BIS 总分小于总样本平均分减去一个标准差(*M*-*SD*)。停止冲动使用反应抑制实验任务(Stop-Signal Task)进行评估，高停止冲动的界定标准：停止–信号反应时间(Stop-Signal Reaction Time, SSRT)大于总体平均数加一个标准差(*M*+*SD*)；低停止冲动的界定标准：SSRT 小于总体平均数减一个标准差(*M*-*SD*)。采用尼古丁依赖量表(FTND)和网络游戏成瘾量表(IAT)评定被试的成瘾行为状况及在连续追踪期间的变化，使用酒精滥用及问题性赌博筛查工具调查在其他成瘾行为方面的卷入程度，使用青少年生活事件量表调查生活应激情况，并调查家庭经济地位及生活质量状况。使用抑郁自评量表(SDS)、焦虑自评量表(SAS)、临床心理症状清单(SCL-90)等评估被试的基本情绪及心理症状。

4.3　研究 3 冲动抑制训练对尼古丁依赖和网络游戏成瘾的干预机制

先前研究提示，采用认知行为训练可以降低成瘾者的冲动性水平并改善成瘾状况，但有限的数量以及一些阴性结果的发现使得其效果仍不明确，且缺乏对非物质成瘾进行冲动干预的对照研究。本研究拟对吸烟成瘾者与网络游戏成瘾者进行 6~12 个月的冲动抑制训练，考察认知行为干预对冲动性与成瘾行为的抑制作用以及潜在的机制。在青少年群体中选取 30~50 名吸烟成瘾者、30~50 名网络游戏成瘾者作为干预被试组(诊断标准同前)，另外选取独立对照组(30~50 名吸烟成瘾者、30~50 名网络游戏成瘾者)，采用延迟干预处理(Delayed-Treatment)，作为认知行为干预的效果参照。认知行为干预(冲动抑制训练)参照以往研究(Bickel et al., 2011; Wesley & Bickel, 2014 ; Wiers et al., 2011)，训练方法主要包括游戏任务、趣味材料阅读、计算机任务等形式，每天 60 分钟，每周 2 次，持续 6~12 个月。使用 Barratt 冲动性量表(BIS)、UPPS-P 冲动行为量表测试被试的特质冲动；使用延迟折扣任务(DDT)、基于奖赏的冲动性决策任务(IGT)测试被试的等待冲动；使用反应抑制任务(Stop-Signal Task)、干扰抑制任务(Stroop Task)测试被试的停止冲动。每个月进行一次冲动性评估，观测实验前后各组的冲动性水平变化情况；并在干预训练开始前和干预训练结束后分别测试被试的冲动神经系统功能变化，具体采用事件相关的 fMRI 设计、结合抑制控制任务(Go/No Go)，考察 dlPFC、IFG、dACC 等感兴趣区(ROI)的激化情况，实验方法及数据处理分析同前。干预训练结束以后，在不同时间点(实验后 1~24 个月)观察各组被试成瘾行为变化状况，考察干预冲动性对成瘾行为的抑制后效。

5 研究预期及探讨

目前在成瘾研究领域，国内外研究者基本认同成瘾疾患防治的关键在于早期识别和干预，有效识别具有较高易感水平和成瘾倾向的重点人群，采用行为或药物干预有可能阻止成瘾行为进一步发展。基于冲动性在成瘾行为发生发展中的重要作用，研究者们试图探索和证实冲动性作为成瘾易感标记的潜在效力及其神经生物机制，为成瘾早期识别和干预提供可能靶点，对成瘾疾患防治具有重要意义。然而，考虑到人类成瘾行为的发生发展过程、逆转变化机制的复杂性，冲动性特质的神经心理结构和维度的多样性，以及成瘾相关的心理学实验设计和混淆因素控制的困难，相关研究要快速实现两个核心目标(其一是明确冲动性作为不同成瘾行为潜在易感标记的有效性及其神经生物基础，其二是明确冲动性作为成瘾干预靶点的有效性及其机制)并非易事。在此方面，我们试图作出一些新的努力：

1)充分结合跨成瘾谱系研究、纵向追踪设计等途径，综合行为学与影像学手段，从物质成瘾与非物质成瘾的比较视角切入，探索冲动性在成瘾行为发展中的调控机制，验证冲动性作为成瘾行为的潜在易感标记的有效性；2)首次从冲动性结构的神经解剖学分类角度，采用混合设计区分不同冲动性水平的个体，进行连续追踪以考察冲动性对成瘾行为发生发展的预测效力；3)同时对物质成瘾与非物质成瘾者进行认知行为训练干预，考察冲动性作为不同成瘾行为潜在干预靶点的确切性及成瘾人群抑制功能重塑的潜在机制。

结合以往研究以及我们前期研究的结果(Yan et al., 2014)，我们初步预期，在物质成瘾(尼古丁依赖)与非物质成瘾(网络游戏成瘾)人群的直接比较当中，可能会出现不同冲动性神经心理结构(即特质冲动、等待冲动、停止冲动)的共同性—特异性(Commonality-Specificity)表现分离的结果。具体来说，在与腹侧纹状体/伏隔核功能紧密相关的特质冲动以及与腹内侧前额叶—腹侧纹状体神经环路功能有关的等待冲动方面，尼古丁依赖人群与网络游戏成瘾人群更可能会同时表现出异常；而在与腹外侧前额叶/前扣带回—背侧纹状体神经环路功能密切相关的停止冲动方面，尼古丁依赖人群更可能会出现异常表现而网络游戏成瘾人群不一定会有异常。据此推论，前述同时在尼古丁依赖人群与网络游戏成瘾人群中表现出来的特质与等待冲动异常特征，可能是一种与成瘾密切相关的共同性神经认知易感因素；而只出现在尼古丁依赖人群中但不出现在网络游戏成瘾人群中的停止冲动异常特征，则可能是一种与长期滥用成瘾物质紧密相关的特异性损伤效应(可参见 Lawrence et al., 2009a, 2009b; Verdejo-García et al., 2008)。

当然，上述研究预期的行为学结果还必须得到神经影像学及追踪研究的证据支持和佐证。假若后续研究的神经影像数据及纵向追踪结果支持行为学结果，那我们可提出初步结论：冲动性可以作为成瘾的潜在易感神经认知标记，但不同冲动性神经心理结构在成瘾行为发生发展过程中存在共同性—特异性的表现分离。以此重要研究结论为基础，我们可以进一步发展出对物质成瘾与非物质成瘾进行差异化干预的认知行为训练方法。比如，对于非物质成瘾(网络游戏成瘾)人群，由于其成瘾障碍的冲动机制是与腹侧纹状体/伏隔核、腹内侧前额叶—腹侧纹状体神经环路的功能障碍有关，具体表现为对即刻奖赏过度敏感、对未来奖赏缺乏延迟满足，那相应的认知行为干预方法应当是与奖赏脱敏及延迟满足的训练主题密切相关。相反，对于物质成瘾(尼古丁依赖)人群，由于其成瘾障碍的冲动机制不仅与腹侧纹状体/伏隔核、腹内侧前额叶—腹侧纹状体神经环路的功能障碍有关，还与腹外侧前额叶/前扣带回—背侧纹状体神经环路的功能障碍有关，其具体表现既有对即刻奖赏过度敏感、对未来奖赏缺乏延迟满足，也有对习惯化的行为不能适当抑制和及时停止的功能问题，因此其相应的认知行为干预方法应同时满足奖赏脱敏及延迟满足的训练主题以及冲动抑制相关的训练主题。成瘾相关的临床治疗实践提示，差异化的干预方法对不同成瘾人群可能具有更好的疗效，如果通过严谨规范的基础研究能找到成瘾早期识别和干预的准确靶点，那对人类成瘾疾患的防治工作而言将是一个划时代的标志，具有极为重要的科学价值。在通往此宏伟目标的道路上，我们深知作为科学探路者中的每一份子都任重道远。

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The neural mechanisms of impulsivity implicated in drug addiction and non-drug addiction

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Abstract: Mounting evidence has demonstrated that impulsivity could be a potential biomarker that plays a crucial role in the development of addictive behaviors, thus impulsivity is considered a possible treatment target for early intervention of addiction. Nevertheless, it remains unclear how the mechanisms underlying the trajectories of impulsivity are involved in drug addiction and non-drug addiction. This project aims to identify the neural mechanisms of impulsivity in both nicotine dependence and internet gaming disorder by combining a direct comparison of drug and non-drug addictive behaviors with longitudinal studies and a cognitive-behavioral intervention study, using neurocognitive tasks and neuroimaging techniques. Firstly, nicotine-dependent individuals and internet gaming addicts would be tested on a series of behavioral tasks of impulsivity as well as in fronto-striatal brain systems using both structured and functional magnetic resonance imaging (fMRI) with a 3T Philips Trio MRI. Then we will move on to investigate the predictive role of impulsivity for nicotine dependence and internet gaming disorder through a 2 to 3 year follow-up study with a large sample of non-addicted adolescents consisting of two groups with either high- or low-levels of impulsivity. Thirdly, a study of 6 to 12 month cognitive behavioral intervention would be conducted on nicotine-dependent individuals and internet gaming addicts to explore the possible effects of reducing impulsivity level on the exacerbation of addictive behaviors. And this study will also evaluate the effects of continuous behavioral training on brain functions in fronto-striatal brain systems through fMRI tests. Totally, these studies should be helpful for shedding light on the possible efficacy of impulsivity as a potential biomarker and treatment target for addictive disorders.

Key words: addiction; impulsivity; inhibitory control; nicotine dependence; internet gaming disorder