

主观记忆减退老年人情节记忆的行为表现及其脑机制*

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摘 要 情节记忆是个体对特定时间、特定地点所经历的特定事件的记忆。主观报告情节记忆下降是主观记忆减退老年人最典型的表现。与健康对照组老年人相比, 主观记忆减退老年人情节记忆下降的速率更快, 罹患老年性痴呆的风险更高, 但其情节记忆加工的脑机制尚不明确。前人研究提示, 主观记忆减退老年人在外在记忆行为尚未出现损伤的情况下, 其大脑情节记忆相关脑区的神经活动已经出现异常。探究主观记忆减退的记忆神经环路关键节点和路径的异常, 揭示神经环路在老年痴呆发生发展中的变化规律, 对深入理解老年痴呆的发病机制有重要的科学意义。同时, 主观记忆减退老年人作为特殊的记忆损伤群体, 对其神经环路的深入探究, 也必将为揭示人类记忆的神经机制做出独特的贡献。

关键词 情节记忆; 主观记忆减退; 老年性痴呆; 脑机制; 老年人

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1 前言

21 世纪以来, 中国人口老龄化问题日益突出, 预计到 2050 年老年人口将超过 4 亿, 占总人口的 30%。认知功能是老年人保持独立的生活能力以及提升生活质量的重要基础。随着年龄增长, 老年人的许多心理功能特别是认知功能出现衰退, 这也是正常老化的必然过程。然而, 与正常的认知功能衰退不同, 有部分老年人会出现快速且持续性的认知能力下降, 最终发展成为老年性痴呆 (Alzheimer's Disease, AD) (Burns & Iliffe, 2009)。AD 是一种神经退行性疾病, 其发生是一个连续的病理生理过程, 并且这个过程在 AD 病人未表现出认知障碍的时期就已经开始发生。在相对较长的一段时间之后, 部分病人才会表现出轻度的认知障碍 (mild cognitive impairment, MCI)。直到

AD 后期, 病人神经元开始大量凋亡, 随之发生的认知损伤也将不再可逆。AD 病理发展的这一特点使得人们对该疾病的早期识别和干预陷入困境。然而, 近年来, 主观记忆减退 (subjective memory decline, SMD) 概念的出现为这一困难的解决提供了新的契机。

主观记忆减退是指部分老年人会自我报告记忆力下降, 但在客观认知测验上的成绩仍处于正常范围之内 (Jessen et al., 2014)。有研究表明, SMD 老年人情节记忆等认知功能下降的速率快于健康对照组, 罹患 AD 的风险更高 (Buckley et al., 2016; Fonseca et al., 2015; Hueluer, Hertzog, Pearman, & Gerstorf, 2015); 并且他们在外在记忆行为尚未出现损伤的情况下, 其大脑的记忆相关脑区的神经活动已经出现异常 (Erk et al., 2011)。这些发现引起了认知老化及痴呆领域研究者的广泛兴趣。Jessen 等人 (2014) 发表在《Alzheimers & Dementia》杂志上的文章初步确立了主观记忆减退研究的理论框架。为了强调对主观记忆减退进行深入研究的意义, 《Journal of Alzheimers Disease》杂志更是于 2015 年专题报道了主观记忆减退期的研究进展, 指出主观记忆减退期是 AD 自然发病过程的最初始阶段 (Rabin et al., 2015; Reisberg &

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Gauthier, 2008)。

因此,探究主观记忆减退的记忆神经环路关键节点和路径的异常,对深入理解老年痴呆的发病机制有极为重要的科学指导意义。同时,对SMD老年人记忆环路的深入探究,也必将为揭示人类记忆的神经机制做出独特的贡献。

2 主观记忆减退是AD最早期症状

值得注意的是,SMD老年人将会以每年6.67%的速率发展为MCI;而大约50%的MCI病人在5年内会发展成为AD(Gauthier et al., 2006);与没有SMD的老年人相比,SMD老年人罹患MCI或AD的风险要高出4.5~6.5倍(Jessen et al., 2010; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010)。因而,SMD老年人是罹患老年性痴呆的高风险人群。

越来越多的影像学证据显示,虽然目前SMD老年人在行为测验上的成绩还没表现出明显下降,但是其大脑可能已经发生了病理性改变(Contreras et al., 2017; 韩璠等, 2015)。与正常对照组老年人相比,SMD老年人 β 样淀粉沉积(Perrotin et al., 2017)和 τ 蛋白指标异常(Colijn & Grossberg, 2015; Garcia-Plata et al., 2016; Snitz et al., 2015a),全脑灰质(Hafkemeijer et al., 2013)和海马的体积减小(Scheef et al., 2012; Stewart et al., 2011)、左侧内嗅皮层厚度降低(Meiberth et al., 2015)。而且,基线的主观记忆损伤能预测接下来的情节记忆相关脑区(海马)的萎缩(Stewart et al., 2011)。最近,Ferreira等人(2017)通过综合临床诊断、认知测验、脑成像和基因相关数据提出了一种测量SMD严重程度的方法;该研究也主张SMD作为健康和MCI的中间状态能够为AD的早期诊断提供重要依据。这些证据支持了主观记忆减退是AD最早期症状的观点,同时也提示对主观记忆减退进行深入研究对于痴呆早期识别和干预的重要意义。

3 主观记忆减退老年人的情节记忆

情节记忆是与人们日常生活关系最密切、发展最高级、成熟最晚的记忆系统,受到了研究者的大量关注。主观报告情节记忆下降是SMD老年人的最典型表现。有研究发现SMD老年人在外在记忆行为尚未出现损伤的情况下,其大脑的记忆相关脑区的神经活动已经出现异常(Erk et

al., 2011)。

3.1 SMD老年人情节记忆的行为表现

情节记忆是人类发展最高级、成熟最晚的外显记忆,且受生理老化影响最大,因而备受认知老化领域和认知神经科学领域的关注(Tulving, 1995)。根据“多重记忆系统”,情节记忆是个体对特定时间、特定地点所经历的特定事件的记忆,将各种特定细节绑定(binding)在一起是其核心特征(Sherry & Schacter, 1987)。而联结记忆(associative memory)即是在传统的内容记忆基础上发展而成的一种直接考察绑定的情节记忆形式(Horn, Kennedy, & Rodrigu, 2018)。

伴随着年龄增长,情节记忆成绩会表现出下降趋势(Mitchell, Johnson, Raye, & D'Esposito, 2000; Old & Naveh-Benjamin, 2008)。根据联结缺陷假说(Associative Deficit Hypothesis, Naveh-Benjamin, 2000),老年人情节记忆下降的原因就在于老年人在产生和提取项目之间的联结能力存在缺陷。联结记忆能力下降不仅是正常老化的显著表现,也是老年痴呆患者最早出现的认知障碍,因此AD也被称为“失连接综合征”。

主观报告情节记忆下降,特别是需要将两个信息绑定的联结记忆存在问题,是SMD老年人最典型的表现,比如SMD老年人会抱怨自己经常忘记物体的摆放位置或不能回忆起某个好朋友的名字等(Lam, Lui, Tam, & Chiu, 2010)。多个横向和纵向研究证据显示,主观记忆成绩与客观认知状况显著相关(Amariglio, Townsend, Grodstein, Sperling, & Rentz, 2011; Cosentino, Devanand, & Gurland, 2018; Hülür, Willis, Hertzog, Schaie, & Gerstorf, 2018; Carrasco et al., 2017; Seo, Kim, Choi, Lee, & Choo, 2017);而且,虽然SMD老年人在情节记忆等认知测验上的成绩与健康对照组老年人没有显著差异,但与健康对照组老年人相比,SMD老年人未来在情节记忆等认知功能上下降的速率更快,罹患AD的风险更高(Fonseca et al., 2015; Hueluer et al., 2015; Horn et al., 2018; Rönnlund, Sundström, Adolfsson, & Nilsson, 2015; Scheef et al., 2012)。比如,Koppara等人(2015)通过追踪调查比较了SMD老年人($N = 1337$)和健康对照组老年人($N = 993$)在8年间认知成绩的变化轨迹,发现SMD老年人在即时和延时回忆任务上成绩下降的速率均要显著快于健康对照组老年人。最近的研究也表明,

SMD 能够预测老年人在单词配对和名字/面容配对任务中的表现(Horn et al., 2018); SMD 老年人表现出更弱的情节记忆练习效应(practice effects, 即通过反复的练习, 测验成绩会相应提高), 在心理运动速度和语言的表现上也更差, 并且有更高比例发展为 MCI 和 AD (Kielb, Rogalski, Weintraub, & Rademaker, 2017)。

另外, 有证据显示, 情节记忆训练能够对 SMD 老年人的记忆状况有一定的改善作用(Boa et al., 2018; Cohen-Mansfield et al., 2015); 最近关于认知训练对 SMD 老年人认知状况提升效果的元分析研究也支持了这一结果(Smart et al., 2017), 说明 SMD 老年人的情节记忆具有一定的可塑性。然而, 也有研究发现, 相对于正常老年人来说, 情节记忆训练对 SMD 老年人的作用更小(Engvig et al., 2014; Pike, Amina, Ben, Sarah, & Kinsella, 2015)。比如, Engvig 等(2014)针对 SMD 和健康对照组老年人开展了情节记忆训练, 来考察 SMD 老年人脑功能的可塑性。结果发现, 经过 8 周的情节记忆训练, (1) SMD 老年人和健康对照组老年人在情节记忆相关脑区的灰质体积上表现出相同程度的提高; (2) SMD 老年人的海马区域体积在个体水平上的变化与更好的情节记忆成绩相关, 但是仅健康对照组老年人在海马区域体积有显著增加, SMD 则没有。Pike 等人(2015)通过口头配对任务(verbal paired associate learning task)对 SMD 老年人的记忆训练效果作出了评估。结果发现, 虽然 SMD 老年人和健康组老年人的任务成绩都有了显著提升, 但是健康组老年人的提升效果比 SMD 老年人的更好。因此, 虽然与健康对照组老年人相比, SMD 老年人在客观认知测验上的表现没有显著下降, 但 SMD 老年人主观报告的记忆力更差, 在未来几年内其情节记忆能力下降的速率会更快, 从情节记忆训练中的获益会更小。

3.2 SMD 老年人情节记忆加工的脑机制

情节记忆主要依赖于内侧颞叶(medial temporal lobe)系统(包括海马、海马旁回和内嗅皮层等脑区)以及前额叶、梭状回和后内侧顶叶等区域(Simons & Spiers, 2003)。海马是记忆功能的核心脑区(Eichenbaum & Fortin, 2003; Moscovitch, Cabeza, Winocur, & Nadel, 2016), 海马的绑定能力降低是情节记忆受损的内在机制(Mitchell et al., 2000)。除了海马的参与外, 情节记忆同样依赖前

额叶的激活(Fletcher, Shallice, & Dolan, 1998; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Umeda et al., 2005)。

虽然 AD 的病因和发病机制尚未明晰, 但其主要的神经病理特征为 β 样淀粉蛋白(Amyloid- β , A β)沉淀形成的细胞外老年斑和 τ 蛋白过度磷酸化形成的神经细胞神经原纤维缠结, 以及神经元丢失伴胶质细胞增生等(Hashimoto, Rockenstein, Crews, & Masliah, 2003; Hernández & Avila, 2007)。随着 SMD 概念的出现, 研究者也开始将关注点放到 SMD 老年人记忆相关脑区的 A β 和 τ 蛋白相关指标的变化上。众多 PET 研究表明, 在认知测验表现正常的老年人中, 主观报告记忆减退越严重的老人, 其 A β 与 τ 蛋白沉积负担越高(Amariglio et al., 2012, 2015; Perrotin, Mormino, Madison, Hayenga, & Jagust, 2012; Horn et al., 2018; Rowe et al., 2010; Snitz et al., 2015b; Swinford, Risacher, Charil, Schwarz, & Saykin, 2018)。根据一项长达 5 年的追踪研究, 在 55 名 SMD 和 94 名 MCI 被试中, 72.4%被试(83%MCI 和 27%SCD)的 A β 与 τ 蛋白相关指标达到 AD 的标准, 这说明相对于正常老年人, 无论是 SMD 还是 MCI 老年人发展成为 AD 的风险更高(Sierra-rio et al., 2015)。Buckley 等(2016)等人更是通过纵向追踪数据表明, 相对于低 A β 蛋白沉积负担的低主观报告记忆减退的老年人, 高 A β 蛋白沉积负担的高主观报告记忆减退老年人的海马体积更小, 同时发展成为 MCI 和 AD 的几率更高。最近的一项研究也表明, 更多的 SMD 与内嗅皮层中越严重的 τ 和 A β 蛋白沉积负担相关(Buckley et al., 2017)。

随着 AD 病程的发展, 大脑神经代谢产物的异常有可能导致结构上的变化。目前, 通过对大脑体积、皮层厚度和皮层表面等形态学上的测量, 研究者们也对 SMD 老年人的大脑结构上的变化进行了探查。大部分研究发现, SMD 老年人在多个不同的脑区出现体积萎缩, 主要集中在内侧颞叶系统, 包括海马、海马旁回和内嗅皮层等脑区(Park et al., 2018; Striepens et al., 2010; Vannini et al., 2017)。Jessen 等人(2006)通过将 AD 患者、MCI 和 SMD 老年人与正常老年人(NC)的海马和内嗅皮层的体积进行比较发现, 随着病程的发展, 内嗅皮层的体积逐渐减小(即 NC > SMD > MCI > AD)。虽然左侧海马体积的减小未达到显著水平,

但是仍然保持着逐渐减小的趋势。后来的研究也发现了相似的结果: Scheef 等人(2012)发现 SMD 老年人的右侧海马体积要比正常老年人的小; 同样, Ryu 等人(2017)结合 MRI 和 DTI 技术也发现, 相对于正常老年人来说, SMD 老年人的内嗅皮层体积更低, 海马的白质结构也出现显著变化。当然, 也有少部分研究并没有发现 SMD 老年人和正常老年人在大脑结构上的显著差异(Tepest et al., 2008; Sluimer et al., 2008), 但是这些结果仍然提示 SMD 老年人的大脑结构表现出变化的趋势。一方面, 出现这些结果的原因可能是不同的研究采用的方法不同, 包括使用的成像技术、比较方法、测量指标上的差异; 另一方面, SMD 老年人在 AD 病程发展中的个体差异可能为不一致的结果作出解释。

在 SMD 阶段, 大脑在结构上已经表现出一定变化, 那么大脑在功能上是否出现异常呢? 通过任务态 fMRI 技术, 大量研究发现 SMD 老年人在情节记忆任务下的激活模式与健康对照组老人存在差异, 主要表现为 SMD 老人在记忆加工的不同阶段都可能表现出额外的激活增强; 但组间差异是否在某些加工阶段出现, 不同研究的结果存在差异(Erk et al., 2011; Hayes et al., 2017; Rami et al., 2012; Rodda, Dannhauser, Cutinha, Shergill, & Walker, 2009)。比如, Rami 等(2012)通过视觉记忆编码任务发现, 与健康对照组老年人相比, SMD 老年人在编码期间楔前叶和后扣带皮层的激活更强。Rodda 等人(2009)发现在情节记忆编码任务下, 虽然 SMD 老人和健康对照组老人都激活了左侧前额叶和小脑, 但主观记忆减退老人还额外激活了左内侧颞叶、顶枕皮层和内侧额叶, 而且 SMD 老人在左侧前额叶的激活增强与其在记忆任务上的成绩显著相关; 类似的, Erk 等人(2011)也发现, 与健康组老年人相比, SMD 老年人在情节记忆回忆(recall)过程中右侧海马活动减弱, 与此同时右侧背外侧前额叶激活增强, 这些结果提示了海马和前额叶等区域活动的功能性改变可能作为一种补偿机制促进了 SMD 老年人记忆成绩的保持。不过, 在该研究中, 两组老年人在编码和再认过程中脑激活模式没有显著差异。最近, Hayes 等人(2017)通过比较 SMD 老年人($n = 23$)和健康对照组老年人($n = 41$)在相继记忆效应(subsequent memory effects, 即在编码任务中击中项目的激活

比遗忘项目的激活更强)上的差异来考察 SMD 老年人在记忆编码加工中的脑激活。结果发现, 与对照组老年人相比, SMD 老年人在枕叶、顶上小叶和后扣带回表现出更低的相继记忆效应; 而且在默认网络相关脑区(包括后扣带回、楔前叶和腹内侧前额叶)表现出更强的负性相继记忆效应。这一结果提示, SMD 老年人编码成功要依赖于独特的神经机制, 这可能反映了其任务指向性注意的整体下降。因此, SMD 老年人情节记忆的回忆过程可能与海马和前额叶活动的功能性改变有关; 而编码和再认等加工过程的神经机制尚且需要未来进一步研究探索。

4 研究小结与展望

4.1 小结

综上所述, 主观记忆减退期是 AD 自然发病过程的最初始阶段, 也是 AD 早期识别和干预最有效的阶段(Rabin et al., 2015; Reisberg & Gauthier, 2008; 尹述飞, 朱心怡, 李娟, 2016)。主观报告情节记忆下降是 SMD 老年人的最典型表现。虽然 SMD 老年人在外在记忆行为尚未出现损伤的情况下, 其大脑记忆相关脑区的神经活动已经出现异常, 但目前关于 SMD 老年人情节记忆加工的脑机制尚不明确。

第一, 与正常老年人相比, SMD 老年人在情节记忆上主要表现为自我报告的主观记忆成绩更差, 而主观记忆成绩与客观记忆测验成绩呈正相关; SMD 老年人同时也表现出更弱的情节记忆练习效应和相继记忆效应; 在未来几年内记忆测验上的行为成绩下降速率更快, 并且有更高的比例发展为 MCI 和 AD。

第二, 关于正常老年人和 MCI/AD 的研究提示前额叶和海马之间的功能性连接是情节记忆(特别是联结记忆)的神经环路。尽管有证据提示 SMD 老年人在情节记忆任务下发生了脑功能性补偿(前额叶激活增强和海马激活减弱), 但并未从功能整合的角度(前额叶-海马之间功能连接)去探讨其情节记忆加工的脑机制。如果采用任务下的激活脑区作为目标脑区, 先考察任务下的功能连接, 然后进一步验证这一功能连接是否在静息状态下仍然存在, 将能更直接客观地揭示 SMD 老年人情节记忆损伤的神经通路。因此, 未来研究可以进一步探索 SMD 老年人的情节记忆表现

是否与其海马与前额叶之间的功能连接异常存在显著关联。

第三, 前人研究提示 SMD 老年人海马和前额叶等脑区活动异常主要影响情节记忆的提取过程(Erk et al., 2011)。目前关于 SMD 老年人情节记忆编码等加工过程的研究结果还存在争议, 有研究认为 SMD 老年人在情节记忆编码过程中楔前叶和后扣带皮层的激活异常(Rami et al., 2012), 也有研究发现 SMD 老年人在情节记忆编码过程中的脑激活模式与健康组老年人没有差异(Erk et al., 2011)。未来研究需要在收集 SMD 老年人在情节记忆编码、存储和提取等各加工阶段的影像学数据的基础上, 进一步深入分析其情节记忆加工过程的脑激活模式及功能连接模式的改变, 以便更深入地理解其情节记忆加工的脑机制。

4.2 研究展望

近年来, 研究者们不仅采用脑成像技术关注与退行性记忆损伤相关的脑激活异常, 也开始关注与这种损伤有关的脑区功能连接(functional connectivity)异常。功能连接技术是考察当活体在静息或进行任务操作时脑区之间的协同活动, 能够测量和比较不同脑区的神经生理活动之间的时间序列相关(Friston, Frith, & Frackowiak, 1993)。对于退行性记忆损伤个体来说, 生理老化和病理性老化的双重影响会导致前额叶和海马均出现功能异常。这种功能异常可能体现在其本身的功能出现障碍, 更可能体现在与其他脑区之间的功能连接上, 特别是这二者之间的功能连接。

然而对介于正常老化和 MCI 患者之间的 SMD 老年人的脑区功能性连接的研究却非常缺乏。Hafkemeijer 等人(2013)通过静息态影像数据的分析, 发现 SMD 老年人在默认网络(default mode network), 包括海马等区域的功能连接相对正常对照组老年人更强。而另一项静息态影像数据显示, 相比健康老年人, SMD 老年人背内侧前额叶网络与右侧海马之间的功能连接水平显著下降(Hu, Harzem, Huang, Weber, & Jessen, 2016), 该研究提示这可能与 SMD 老年人情节记忆系统损伤有关。Contreras 等人(2017)通过考察 SMD、MCI 和 AD 老人在静息态下脑功能连接模式发现, 被试在情节记忆任务上的成绩与额顶网络-默认网络功能连接强度呈正相关。

遗憾的是, 关于 SMD 老年人在情节记忆加工

过程中脑区功能性连接的研究几近真空地带。目前已有研究尝试利用这种技术探讨与 AD/MCI 有关的脑区功能连接异常(Grady, Bernstein, Beig, & Siegenthaler, 2002; Greg et al., 2007; Wang et al., 2006)。比如 Grady 等(2002)发现, 在面孔记忆任务中 AD 患者海马与前额叶皮层的功能性连接丧失。MCI 在情节记忆提取任务中, 海马与前额叶等脑区的功能性连接减弱(Hampstead, Khoshnoodi, Yan, Deshpande, & Sathian, 2016), 而与更弥散区域的连接加强, 以补偿上述连接的减弱(Bai et al., 2009)。这些结果支持了海马与前额叶功能性连接在退行性记忆损伤病人中受损的假设。

SMD 老年人之所以在记忆相关的行为测验成绩上没有表现出明显下降, 很可能的原因在于他们更容易发生脑活动的功能性补偿(Jessen et al., 2014)。Erk 等人(2011)的研究虽然采用面孔-职业绑定的情节记忆任务初步发现了 SMD 老年人的神经性补偿机制, 但是该研究仅从前额叶和海马的激活变化的角度进行分析。而 SMD 老年人情节记忆损伤既可能与前额叶和海马自身功能相关, 也可能与这两个区域之间的功能连接有关。而且, 该研究在工作记忆任务下没有发现相应的补偿, 这也提示在情节记忆任务下去考察 SMD 老年人的脑区功能连接, 对于阐明情节记忆加工的脑机制及痴呆的早期识别意义重大。如果采用任务下的激活脑区作为目标脑区, 先考察任务下的功能连接, 然后进一步验证这一功能连接是否在静息状态下仍然存在, 将能更直接客观地揭示 SMD 老年人联结记忆损伤的神经通路机制。

主观记忆减退是老年痴呆的最初始阶段, 而 SMD 老年人最典型的表现就是主观报告情节记忆下降。探究主观记忆减退的记忆神经环路关键节点和路径的异常, 揭示神经环路在老年痴呆发生发展中的变化规律, 对深入理解老年痴呆的发病机制, 早期识别、并提供合适有效的干预方案, 从而降低老年痴呆的发病率、延缓老年痴呆发展的进程, 有及其重要的科学指导意义。同时, SMD 老年人作为特殊的记忆损伤群体, 对其神经环路的深入探究, 也必将为揭示人类记忆的神经机制做出独特的贡献。

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Episodic memory performance and underlying brain mechanisms in elderly with subjective memory decline

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Abstract: Episodic memory (EM) is the collection of past personal experiences that have occurred at a particular time and place. Subjective decline in EM is reported in the elderly with subjective memory decline (SMD). The elderly with SMD have a faster rate of EM decline and a higher risk of developing Alzheimer's disease (AD) than do healthy controls. However, the brain mechanisms of episodic memory impairment in SMD are unclear. Previous studies suggest that even when memory performance has no observable deficits, the brain structure and function associated with EM have been abnormal in SMD. Two further studies are of vital scientific significance for understanding the pathogenesis of AD. One is to explore the abnormal key nodes and paths of memory neural circuits in SMD. The other is to reveal the changes in the neural circuits in the progression of AD. In addition, considering that the elderly with SMD are a special group with memory impairment, an in-depth investigation into the neural circuits in this group, will make a unique contribution to revealing the neural mechanism of human memory.

Key words: episodic memory; subjective memory decline; Alzheimer's disease; brain mechanisms; elderly