成人注意缺陷多动障碍静息态功能连接分析

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【摘 要】目的：注意缺陷多动障碍(Attention Deficit Hyperactivity Disorder, ADHD)是一种在儿童期多发的疾病，对ADHD的研究也主要集中在儿童期疾病，却往往忽略了占有相当大比例的成年人，大部分的成人患者都是从儿童期疾病发展而来的，因此进一步研究成人期的疾病信息对于ADHD的致病机理和疾病在成长发育中的延续变化具有显著的意义。本文旨在通过静息态功能磁共振成像的方法从功能连接的角度来研究成人患者在情感和认知方面存在的脑区异常，并试图对比疾病在儿童期和成人期的差异。**对象与方法：**实验对象有成人ADHD患者组和成人正常对照组，分别20例，年龄20岁~50岁，均无其他人口统计学差异。分别获取两组被试的静息态功能磁共振数据，预处理后基于成人ADHD前扣带回(ACC)头尾部也存在情感和认知功能分离的假设，均选取两组被试在MNI坐标下的ACC头尾部两个感兴趣种子区域ROI1(5, 2, 46)和ROI2(5, 34, 14)，并进行感兴趣区域与全脑的功能连接计算以及功能连接的单样本、双样本*t*检验的统计分析。从统计分析可以得出两组被试的两个感兴趣区域分别与全脑显著相关的脑区分布，患者组与正常对照组在相应的功能连接结果中的差异脑区以及*t*值峰值坐标位置。**结果与结论：**在单样本*t*检验中，ADHD成人患者组和正常被试组ACC头尾部的两个感兴趣位点与全脑的功能连接中存在情感和认知功能分离的现象，即背侧尾部区域与运动辅助区等认知执行相关脑区相关，腹侧头部区域则参与下前扣带回等情感过程。在双样本*t*检验中，ADHD成人患者组相对于正常组在两个感兴趣区域与情感相关的脑区功能连接中，部分脑区连接增强部分脑区连接减弱；与运动相关脑区的功能连接没有明显差异；成人ADHD组的ACC头尾部与部分注意网络区域功能连接增强，与默认网络部分区域功能连接减弱。因此，ACC头尾部在人类情感和认知过程中存在重要影响，而且成人和儿童ADHD患者的ACC头尾部与全脑功能连接可能存在显著意义的差异。

【关键词】成人；注意缺陷多动障碍；前扣带回；头尾部；静息态功能磁共振；功能连接；功能分离

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Resting-state functional connectivity analysis of adult attention deficit hyperactivity disorder

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Abstract: Objective Attention deficit hyperactivity disorder (ADHD) is a kind of common disease in young children, so the researches mainly focus on the ADHD in childhood. However, a large number of adults with ADHD is often ignored. Most adult patients has developed ADHD since childhood, so further research on adult ADHD is of remarkable significance for its pathogenic mechanism and changes along with ages. From the point of functional connectivity, resting-state functional magnetic resonance imaging (RS-fMRI) was applied to study on the abnormal conditions of brain regions of adult patients in emotion and cognition, and to contrast the differences between ADHD in adult and childhood. **Methods** There were adult ADHD group and normal group, each group of 20 cases, aged 20-50 years old. And there were no other demographic differences in these two group. The RS-fMRI data of these two groups were obtained. Based on the hypothesis that the head and tail of the anterior cingulate cortex (ACC) of adult with ADHD showed emotional and cognitive functional separation, the

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two seed regions of interest (ROIs) at the head and tail of ACC in both groups, ROI1 (5, 2, 46) and ROI2 (5, 34, 14) in MNI coordinate, were selected to calculate the functional connectivity between ROIs and the whole brain and to statistically analyze the results of one-sample T test and two-sample T test of functional connectivity. According to the statistical analysis, the brain regions significantly correlated to the selected ROIs could be found. The brain regions with different functional connectivity between adult ADHD group and normal group were obtained. And the coordinate of T peak value was also obtained. **Results and conclusion** The one-sample T test showed that emotional and cognitive functional separation existed in the functional connectivity between ROIs at the head and tail of ACC and whole brain in these two groups. Dorsal region of ACC tail and supplementary motor area were associated with the brain region related to cognition and process, while ventral region of ACC head was involved in emotional process of anterior cingulate and so on. The two-sample T test showed that the functional connectivity between the ROIs and some brain regions related to emotion in adult ADHD group was stronger than that in normal group, while the functional connectivity in other emotional areas in adult ADHD group was weaker than that in normal group. No obvious differences were found in the functional connectivity in the brain areas involved motor. For adult patients, the head and tail of ACC had a stronger connection to some areas of dorsal attention network and weaker connection to the areas of default network. ACC is of great importance on human emotion and cognition. The functional connectivity between the head and tail of ACC and the whole brain shows significant differences between the adult patients and young patients.

Key words: adult; attention deficit hyperactivity disorder; anterior cingulate cortex; resting-state; rs-fMRI; functional connectivity; functional separation

前 言

人们普遍认为注意缺陷多动障碍(Attention Deficit Hyperactivity Disorder, ADHD)是儿童期专属的一种疾病，随着年龄的增长这种病症会慢慢消失。但是越来越多的临床案例表明大量的多动儿症状会延续到成人时期[1]，而且儿童期ADHD的最明显症状“多动”有随着年龄增加而减弱的趋势，在成人中更偏向内心不安的主观体验[2-3]。现在，已经有很大比例的成人ADHD患者受到疾病的困扰。如果能够做到早期诊断和预防，充分了解患病机制，对于防止和降低ADHD对患者生活带来的影响有重大意义[4]。

利用静息态功能磁共振(rs-fMRI)对儿童ADHD的研究已经获得了很多有价值的结论。本文在已有的儿童ADHD的研究基础上，对成人ADHD患者和正常对照组的rs-fMRI数据进行种子点功能连接的分析[5]，期望找到有价值的致病机制信息。

1 功能连接数据处理

本文中数据均来自公开的供研究的千人数据集Functional Connectomes Project（http://www.nitrc.org/projects/fcon_1000）。ADHD患者组数据和正常组数据均采自纽约，患者年龄20岁~50岁，均有通过自我测试和临床诊断被确诊为ADHD患者的详细数据，共22人。每个被试者数据均包括EPI序列得到T_2加权图像。功能项数据参数为：TR=2000 ms，Slices=39，Timepoints=192。正常对照组年龄18岁~46岁，功能项数据的TR=2000 ms，Slices=33，Timepoints=175。数据性别和惯用手均无显著性差异。

（1）预处理步骤使用基于spm8的DPARSF软件（http://www.restfmri.net/forum/taxonomy/term/35）进行，包括时间点去除、时间层校正、头动校正、空间标准化、4 mm高斯平滑、0.01 Hz~0.08 Hz带通滤波滤掉高频段的呼吸心跳噪声和低频段的噪声。

（2）功能连接的计算(FC)：对健康成人的前扣带回(ACC)研究时，Margulies等[6]选择了ACC上面16个种子点感兴趣区域(ROI)(图1)，结果显示，ACC腹侧头部i5-i9和与情感相关的脑区边缘系统有正的功能相关性；而位于背侧尾部的(i1, i2, s1, s2)与感觉运动相关的区域显示有正的功能连接，与边缘系统的脑区有负的连接。额-顶区是与感觉运动有关的区域。本文中，根据文章中提到的MNI坐标分别选取两组中ACC的背侧尾部位点(5, 2, 46)和腹侧头部的位点(5, 34, 14)作为两个感兴趣种子区域，分别记为(ROI-1)和(ROI-2)，半径均为r=3.5 mm。在DPARSF软件中，把做完预处理的数据去除常见的默认协变量，然后进行FC计算[6]。

2 统计分析与结果

用REST软件(http://restfmri.net/forum/index.php)分别对各个组别进行功能连接单样本(P<0.01，AlphaSim校正)、双样本t检验以及最后的结果可视化(P<0.01，AlphaSim校正)。然后，对ADHD与正常

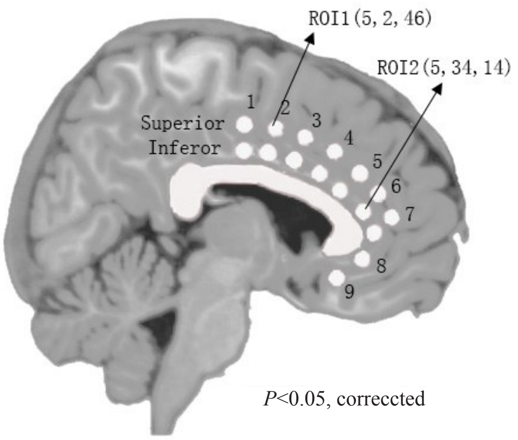


图 1　感兴趣种子区域的选择

Fig.1　Choices of regions of interest (ROI)

16 ROIs of anterior cingulate cortex(ACC), r=3.5 mm. Superior means dorsal, while inferior means veutro (s1, s2···, i1, i2···)

对照组进行双样本 *t* 检验（*P*<0.05，AlphaSim 校正），取不小于85个连续体素体积为有效显著区。

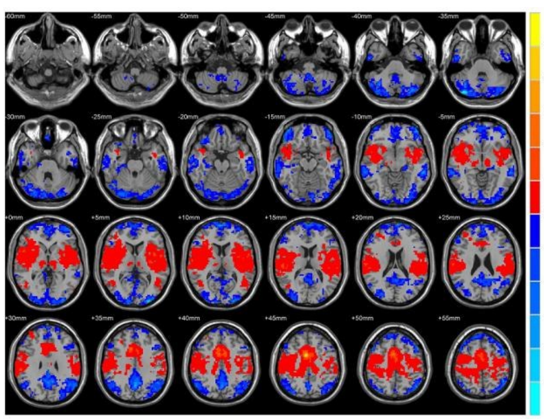
2.1　单样本 *t* 检验结果及分析

（1）ADHD组和正常组在ACC尾部（ROI-1）单样本 *t* 检验：*t* 检验（*P*=0.01）中，ADHD被试组与正常被试组在ACC尾部位点的功能连接结果类似，如图2所示。正的功能连接区域为：运动辅助区（*t* 值和团块最大）、额下回、额中回、颞中回、岛叶、边缘叶、顶下小叶、丘脑；负的功能连接：双侧小脑后叶、颞上回、颞中回、颞下回、海马、眶额叶、枕叶、楔前叶、角回。

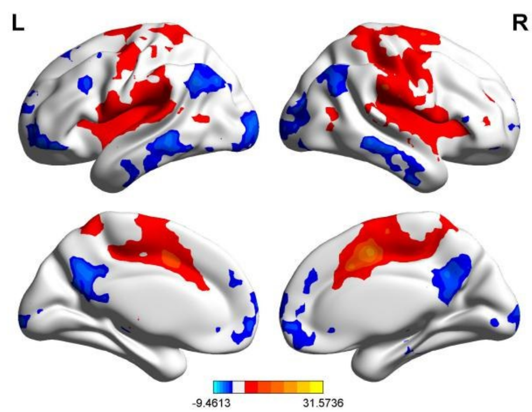
（2）ADHD组和正常组在ACC头部（ROI-2）单样本 *t* 检验：*t* 检验（*P*=0.01）中，ADHD被试组与正常被试组在ACC头部位点的功能连接结果类似，如图3所示。正的功能连接：下前扣带回（团块最大）、梭回、颞叶、丘脑、前岛叶及眶额叶；负的功能连接：双侧前额叶、小脑、枕叶、中央旁小叶、海马旁回。

2.2　双样本 *t* 检验结果及分析

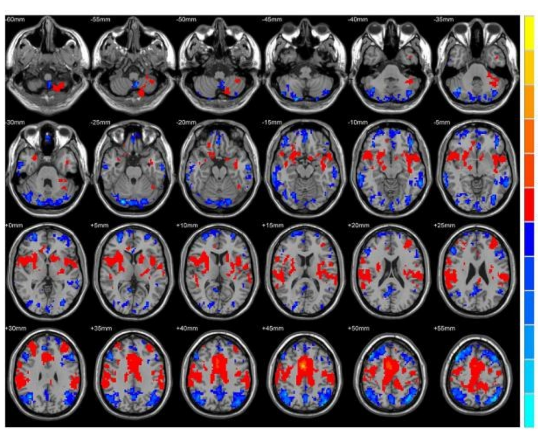
ACC头尾部种子区域的双样本 *t* 检验的功能连接结果如图4所示，列表的表述如表1和表2所示。



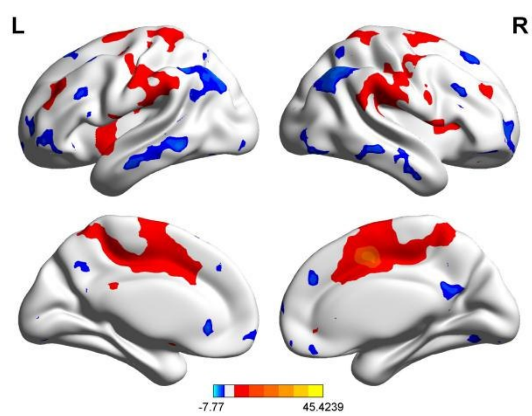
a: ADHD functional connection on layers



b: ADHD functional connection on gray cortex



c: Normal functional connection on layers

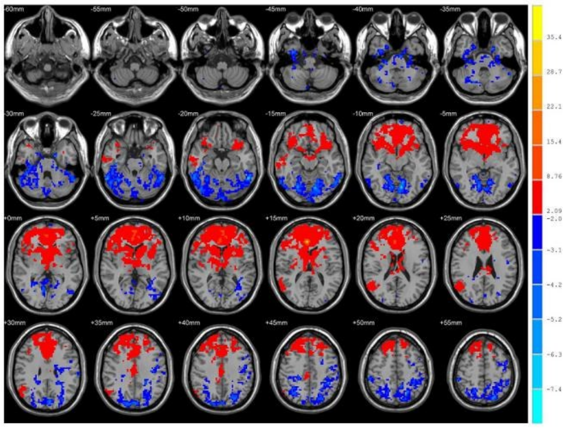


d: Normal functional connection on gray cortex

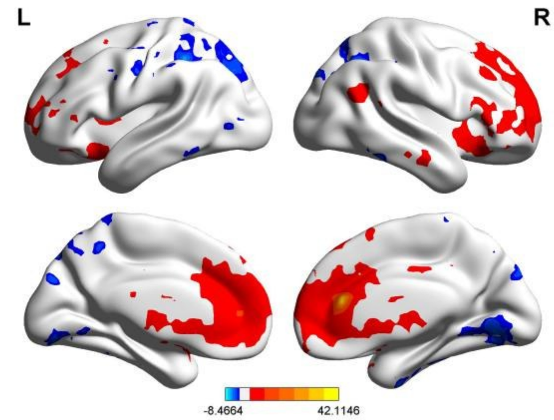
图 2　ADHD患者和健康人ACC尾部位点的功能连接图

Fig.2　The function connections in the ACC tail region of the patient and the healthy

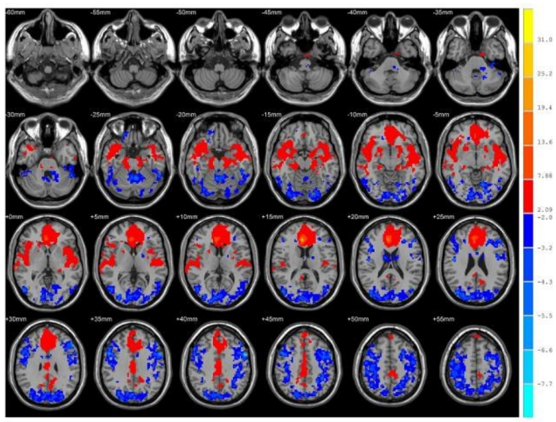
Note: ADHD: Attention deficit hyperactivity disorder. The red was positive functional connection area, while the blue was negative functional connection area



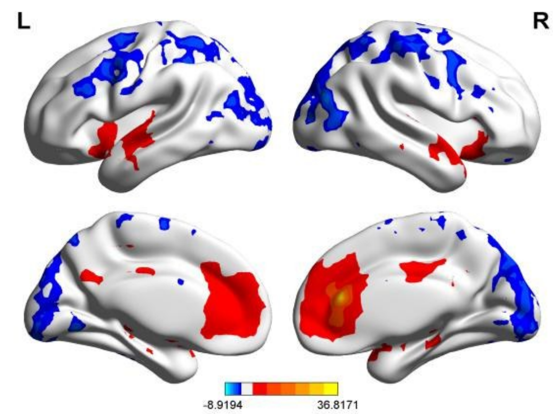
a: ADHD functional connection on layers



b: ADHD functional connection on gray cortex



c: Normal functional connection on layers



d: Normal functional connection on gray cortex

图 3　ADHD患者和健康人ACC头部位点的功能连接图

Fig.3　The function connections in the ACC head region of the patient and the healthy

Note: The red was positive functional connection area, while the blue was negative functional connection area

本文中，与ROI-1（P=0.05）存在功能连接增强的脑区有：右侧顶叶、右侧顶上回、左右侧岛叶、颞叶；功能连接减低的脑区为：小脑后叶、左眶内额上回、右内侧额上回、右眶内额中回、左侧额中回、左侧后扣带回。与ROI-2（P=0.05）存在功能连接增强的脑区有：右侧枕下回、右侧顶上回、右侧中央前回；功能连接下降的脑区为：左侧海马旁回、右侧海马旁回、左侧颞中回、右侧颞上回、前扣带和旁扣带回、额中回（工作记忆）、左侧楔前叶、内侧和旁扣带回。

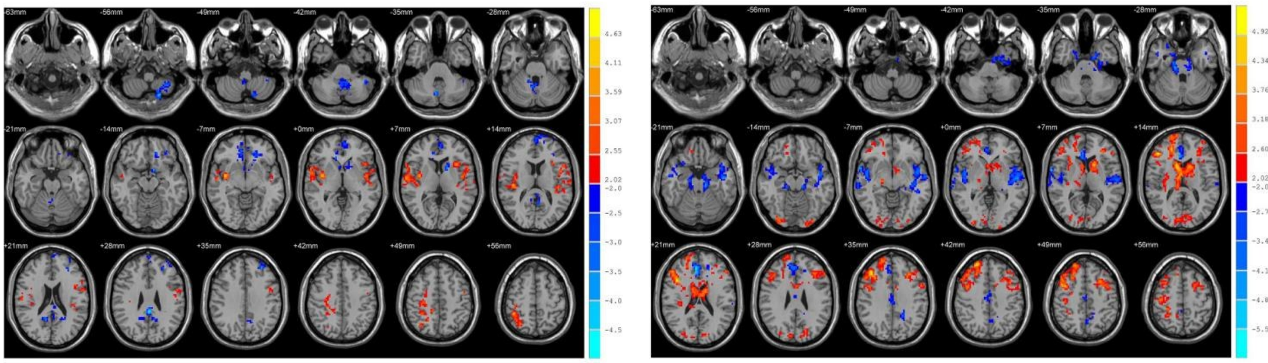
3 讨论与总结

研究证实前扣带回皮层（Anterior Cingulate Cortex, ACC，包括Brodman 24、25和32区）具有明显的行为监测功能[3,7]，能够及时地在信息处理过程中出现反应冲突和错误时进行调整和分配注意资源[8-10]。同时，ACC在多种认知功能中都起重要的调控作用，在ADHD研究中是一个重要的、值得关注的脑区[6,11-13]。

本文结果与结论如下：

（1）在单样本检验中，ADHD成人患者的ACC头尾部也存在认知与情感功能分离的观点，即背侧尾部是与认知过程相关的区域，腹侧头部则参与情感过程[8,10,14]。与尾部呈现正的功能连接的脑区有运动辅助区（t值和团块最大）、额下回、额中回、颞中回、岛叶、边缘叶、顶下小叶、丘脑等，这些脑区与感觉、运动及执行功能相关；而与双侧小脑后叶、颞上回、颞中回、颞下回、海马、眶额叶、枕叶、楔前叶、角回等与情感相关及默认网络的脑区有负的功能连接[2,13,15]。头部与下前扣带回（团块最大）、梭回、颞叶、丘脑、前岛叶及眶额叶等有正的功能连接；与双侧前额叶（团块最大）、小脑、枕叶、中央旁小叶、海马旁回呈现负的功能连接。

（2）在双样本检验中，成人ADHD患者的ACC尾部与岛叶、颞叶、顶叶等脑区连接增强，与小脑后叶、眶内额上回、眶内额中回、后扣带回连接减弱。ACC



a: Two-sample t test of ACC tail (ROI-1)　　　　b: Two-sample t test of ACC head (ROI-2)

图4 ACC头尾部双样本T检验

Fig.4 Two-sample *t* test for the tail and head of ACC

In the two-sample T tests, *P*<0.05 (correction), Voxel volume>85; BA: Brodmann brain regions; Red means T>0: FC in ADHD group was higher than that in the normal group; Blue means T<0, FC in ADHD group was lower than that in the normal group

表1 ADHD与正常组(ROI-1)双样本*t*检验结果

Tab.1 Two-sample *t* test results in ADHD group and normal group (ROI-1)

Brain anatomical regions	MNI coordinate (mm)			BA	Peak cluster (mm^3)	*t* value
	X	Y	Z			
Left cerebellum posterior lobe	-21	-69	-60	-	1728	-4.538 3
Right cerebellum posterior lobe	6	-69	-33	-	2430	-4.659 7
Frontal_Sup_Orb_L	-15	39	-15	11	702	-3.525 0
Olfactory_R	3	12	-3	34	243	-3.629 6
Insula_RTemporal_Sup_R	39	-6	-3	6	3159	5.152 1
Insula, Superior temporal gyrus (L)	-45	-6	-3	6	3807	4.012 6
Frontal_Med_Orb_R	6	42	-9	6	2268	-4.066 6
Frontal_Sup_Medial_R	3	66	12	10	729	-3.549 9
Frontal_Mid_L	-30	42	36	9	1890	-3.810 3
Cingulum_Post_L	0	-39	27	31	1080	-4.552 5
Right parietal lobe	24	-30	45	3	2538	3.605 1
Parietal_Sup_R	42	-45	60	7	2592	4.104 5

头部与枕下回、顶上回、中央前回等连接增强,与海马旁回、颞中回、颞下回、楔前叶、内侧和旁扣带等区域连接减弱。因此可见患者ACC头部和尾部均存在与部分情感相关的脑区连接增强和减弱的区域,在运动相关的脑区则不存在明显差异[7, 16]。这个结果区别于在儿童期疾病研究中发现的单纯地与情感区域和运动区域功能连接增强的发现。推测是成人相对于儿童在多动、情绪化表现方面症状减弱的原因。

(3)注意缺陷分析:注意缺陷是ADHD很明显的表现。在解剖结构中的大脑顶叶、额叶、中央前沟等与注意过程相关,它主要体现在抑制无关的刺激以及对持续注意过程的维持[2, 4, 14]。本文双样本检验中,成人ADHD组的ACC尾部与大脑右侧的额叶内侧功能连接降低、与右侧顶叶功能连接增强,ACC头部与顶上回功能连接增强。这两个脑区都是注意网络的组成,因此可以认为,静息态下ACC与注意网络连接的异常改变可以推测与成人患者多数存在的内心不安、敏感相关。另外在患者的ACC头部与楔前叶、扣带回后部、中央前回的连接也降低,可以认为其与默认网络的连接也出现异常[9, 11, 17],因此推测默认网络与ACC的连接异常可能也是成人患者中存在的普遍现象。

综上所述,通过对rs-fMRI图像ACC头尾部与全脑功能连接分析,我们得出成人患者与健康人的大脑在ACC皮层确实存在情感和认知方面的差异。无论对于儿童ADHD患者还是成人ADHD患者,ACC的连接都具有研究意义,或许可以将其与儿童患者的研究结合起来探索ADHD从儿童到成人的纵向转化过程,为ADHD的早期预防和治疗提供有效信息。

表2 ADHD 与正常组(ROI-2)双样本 t 检验结果

Tab.2 Two-sample t test results in ADHD group and normal group (ROI-2)

Brain anatomical regions	MNI coordinate(mm)			BA	Peak cluster (mm³)	t value
	X	Y	Z			
ParaHippocampal_L	-12	-24	-21	36	513	-4.4394
ParaHippocampal_R	15	-27	-27	-	1269	-4.591
Temporal_Mid_L	-45	-12	-21	22	6750	-5.0087
Temporal_Sup_R	66	3	3	22	6561	-5.0625
Occipital_Inf_R	30	-93	-12	18	1242	3.7698
Cingulum_Ant_R Middle Frontal Gyrus	6	33	18	9	1512	-6.195
Precuneus_L	-21	-42	33	5	1269	-4.3534
Cingulum_Mid_R	6	-15	45	24	1404	-3.5233
Parietal_Sup_R Postcentral_R	27	-36	54	7	189	3.7032
Precentral_R	36	-15	54	6	3294	3.7742

Note: BA: Brodmann brain regions; MNI coordinate: Standard brain space provided by Montreal neurological institute

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