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Fronto-striatal effective connectivity of working memory in adults with cannabis use disorder

Liangsuo Ma^{a,b,*}, Joel L. Steinberg^{a,c}, James M. Bjork^{a,c}, Lori Keyser-Marcus^{a,c}, Jasmin Vassileva^{a,c}, Min Zhu^d, Venkatesh Ganapathy^c, Qin Wang^e, Edward L. Boone^e, Sergi Ferré^f, Warren K. Bickel^g, F. Gerard Moeller^{a,c,h,i}

^aInstitute for Drug and Alcohol Studies, Virginia Commonwealth University (VCU), 203 East Cary Street, Suite 202, Richmond, VA 23219, USA

^bDepartment of Radiology, Virginia Commonwealth University (VCU), Richmond, VA, USA

^cDepartment of Psychiatry, Virginia Commonwealth University (VCU), Richmond, VA, USA

^dRadiology Department, Mu Dang Jiang Medical University, Mu Dang Jiang, Hei Long Jiang, China

^eDepartment of Statistical Sciences and Operations Research, Virginia Commonwealth University (VCU), Richmond, VA, USA

^fIntegrative Neurobiology Section, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD, USA

^gDepartment of Psychology, Virginia Tech, Roanoke, VA, USA

^hDepartment of Pharmacology & Toxicology, VCU, Richmond, VA, USA

ⁱDepartment of Neurology, VCU, Richmond, VA, USA

Abstract

Previous working memory (WM) studies found that relative to controls, subjects with cannabis use disorder (CUD) showed greater brain activation in some regions (e.g., left [L] and right [R] ventrolateral prefrontal cortex [VLPFC], and L dorsolateral prefrontal cortex [L-DLPFC]), and lower activation in other regions (e.g., R-DLPFC). In this study, effective connectivity (EC) analysis was applied to functional magnetic resonance imaging data acquired from 23 CUD subjects and 23 controls (two groups matched for sociodemographic factors and substance use history) while performing an n-back WM task with interleaved 2-back and 0-back periods. A 2-back minus 0-back modulator was defined to measure the modulatory changes of EC

*Corresponding author at: Department of Radiology, Virginia Commonwealth University, 203 East Cary Street, Suite 202, Richmond, VA 23219, USA. Liangsuo.ma@vcuhealth.org (L. Ma).

Conflict of interest

The authors declare that they have no conflict of interests.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from all participants.

corresponding to the 2-back relative to 0-back conditions. Compared to the controls, the CUD group showed smaller modulatory change in the R-DLPFC to L-caudate pathway, and greater modulatory changes in L-DLPFC to L-caudate, R-DLPFC to R-caudate, and R-VLPFC to L-caudate pathways. Based on previous fMRI studies consistently suggesting that greater brain activations are related to a compensatory mechanism for cannabis neural effects (less regional brain activations), the smaller modulatory change in the R-DLPFC to L-caudate EC may be compensated by the larger modulatory changes in the other prefrontal-striatal ECs in the CUD individuals.

Keywords

Cannabis use disorder; Marijuana dependence; DCM; Effective connectivity; Working memory; Prefrontal-striatal circuit

1. Introduction

The expanding decriminalization of cannabis in the United States has brought forth debate and scrutiny regarding potentially detrimental cognitive effects of cannabis. Both animal (Rubino and Parolaro, 2014) and human (Schweinsburg et al., 2008a; Martin-Santos et al., 2010; Wrege et al., 2014) studies show that cannabis use disorder (CUD) is associated with altered working memory function (Solowij and Battisti, 2008; Crean et al., 2011; Schoeler and Bhattacharyya, 2013) and other cognitive dysfunction (Quickfall and Crockford, 2006; Bhattacharyya et al., 2012; Batalla et al., 2013). Improvement of cognitive function is a potential treatment target for CUD (Sofuoglu et al., 2010) and other substance use disorders (SUDs) (Sofuoglu, 2010; Sofuoglu et al., 2013). Thus, in light of the increasing cannabis use in the United States (SAMHSA: <https://www.samhsa.gov/>), a better understanding of the neurobiological mechanisms underlying altered cognitive functions in CUD would be helpful for improving existing treatment and developing new strategies for treatment.

Working memory (WM), defined as the ability to retain information temporarily for further processing, is thought to be a core component of cognition that underlies performance of a number of lower-order specific cognitive functions (Funahashi, 2017). Several functional magnetic resonance imaging (fMRI) studies investigating WM in CUD have been published (Jacobsen et al., 2004; Kanayama, et al., 2004; Jager et al., 2006; 2010; Padula et al., 2007; Schweinsburg et al., 2005; 2008b; 2010; Nestor et al., 2008; Becker et al., 2010; Smith et al., 2006; 2010; Cousijn et al., 2014a; 2014b) and reviewed (Lundqvist, 2005; Jager and Ramsey, 2008; Solowij and Battisti, 2008; Batalla et al., 2013; Crane et al., 2013; Bossong et al., 2014; Broyd et al., 2016; Weinstein et al., 2016). Although exceptions have been noted (Cousijn et al., 2014a; 2014b), the majority of these studies found altered regional activation in the CUD individuals during the working memory tasks. Relative to the controls, the CUD subjects had lower activation in the right hippocampus (Jacobsen et al., 2004), bilateral middle frontal cortex, right dorsolateral prefrontal cortex (DLPFC) and occipital cortex (Schweinsburg et al., 2008b), right precentral gyrus (Schweinsburg et al., 2010); and greater activation in bilateral superior, middle, and inferior frontal gyrus or ventrolateral prefrontal cortex (VLPFC), right superior temporal gyrus, anterior cingulate gyrus, right precentral

gyrus, caudate, and putamen (Kanayama et al., 2004), right claustrum, putamen, caudate, thalamus, globus pallidus, insula, globus pallidus, right precuneus, superior parietal lobule, postcentral gyrus, left superior parietal lobule, precuneus (Padula et al., 2007), right posterior parietal cortex (Schweinsburg et al., 2008b), right inferior frontal gyrus (or VLPFC), left middle frontal gyrus, and right superior temporal gyrus (Smith et al., 2010), left inferior frontal gyrus (or VLPFC), left precentral cortex, left DLPFC, and anterior cingulate cortex (Jager et al., 2010), medial and left superior prefrontal cortices, and bilateral insula (2010), and left superior parietal lobe (Becker et al., 2010). In addition, during a task involving learning and memory, CUD individuals showed lower activation in the right superior temporal gyrus, right superior frontal gyrus, right middle frontal gyrus and left superior frontal gyrus and greater activation in the right para- hippocampal gyrus than the controls (Nestor et al., 2008). The greater brain activations were consistently interpreted as being related to a compensatory mechanism for cannabis adverse neural effects (less regional brain activations). The hyperactivity was not limited to the WM task networks. Additional regions, such as the right superior temporal gyrus found by Smith et al. (2010), were recruited for compensation. These published WM studies have all investigated regional brain activation, and there is a paucity of brain connectivity studies in CUD working memory research (Weinstein et al., 2016).

Theoretically, the transition from voluntary to addictive/problematic/compulsive use may result in part from an imbalance between two separate and interacting systems (“dual-system theory”): a pre- frontal cortex (or reflective) system, and a striatum (or impulsive) system (Bechara, 2005; Bickel et al., 2007; Everitt et al., 2008). Such an imbalance has been theorized to contribute to the compulsive substance use and loss of control in SUDs (Bechara, 2005; Bickel et al., 2007; Everitt et al., 2008). Specifically, the progression of SUDs parallels a transition from prefrontal cortical to striatal control over drug seeking and a transition from recruitment of ventral to more dorsal sections of the striatum during instrumental behavior (Everitt et al., 2008). In the dual-system theory, DLPFC and VLPFC are thought to underlie the reflective system, and the striatum the impulsive system. Consistently, the majority of the previous WM fMRI studies reviewed above suggested altered prefrontal-striatal neural networks in the CUD, involving DLPFC, VLPFC, and striatum. Specifically, the CUD individuals showed lower activation in R DLPFC than the controls, likely reflecting the reduced effect of R DLPFC in the CUD individuals. On the other hand, the CUD individuals showed greater activation in L DLPFC, L VLPFC, R VLPFC, and R striatum than the controls, likely reflecting that these prefrontal regions may be related to compensation for the reduced R DLPFC activation in the CUD individuals.

Although the dual-system theory was developed in the context of reward processing, the DLPFC to striatum connectivity and the VLPFC to striatum connectivity are involved in higher order processes which are not directly related to rewards, e.g., working memory (Ma et al., 2014) and inhibition (Ma et al., 2015). DLPFC, VLPFC, and caudate and putamen regions of the striatum have been consistently found to be active during working memory tasks (see Wager and Smith (2003) and Owen et al. (2005) for review). Prefrontal-striatal circuits have been suggested as potential therapeutic targets for SUDs (Garavan et al., 2013; Kravitz, et al., 2015) and overlap with other theorized neuro- circuits underlying SUDs (Koob and Volkow, 2016). Among the various cortico-striatal circuits (Lawrence et al.,

1998), the DLPFC to caudate and the VLPFC to caudate circuits are particularly relevant to the present study, which used pictures as stimuli in the WM task (see the Methods section). DLPFC connects to the dorsal-posterior part of the caudate, and VLPFC connects to ventral part of the caudate (Yeterian and Pandya, 1991; Leh et al., 2007). The different functional contributions of these two loops may be explained by the different roles of DLPFC and VLPFC in working memory. As reviewed by Leh et al. (2010), the DLPFC likely plays a role in divided attention and monitoring of information within working memory (Kostopoulos and Petrides, 2003; Petrides, 2005; Rizzuto et al., 2005), and the VLPFC likely play a specific role in memory retrieval (Kostopoulos and Petrides, 2003; Petrides, 2005).

Based on previous studies and in light of the dual-system theory, we hypothesized that during WM, the DLPFC to caudate circuit and the VLPFC to caudate circuit would be altered in CUD individuals. To that end, we used dynamic causal modeling (DCM) (Friston et al., 2003) to measure DLPFC to caudate and VLPFC to caudate effective (directional) connectivities (Friston, 2011). DCM has two major advantages over other effective connectivity (EC) techniques. First, disease or substance exposure could affect neurovascular coupling and/or hemodynamic responses (Iannetti and Wise, 2007). In DCM, the parameter for the ratio of intra- and extravascular signal in the hemodynamic model of DCM is estimated from the observed fMRI signal (Stephan et al., 2007). Thus, DCM accounts for the individual difference in neurovascular coupling and/or hemodynamic responses. Second, DCM can measure EC during specific experimental conditions of the task, such as the 2- back and 0-back conditions of the n-back working memory task that were used in the present study. As described in the Methods section, we measured modulatory change in EC, defined as the change in EC during the 2-back condition relative to that during the 0-back condition, reflecting differential effects of WM demand.

Based on the functional magnetic imaging (fMRI) data (downloaded from Human Connectome Project, Van Essen, et al., 2013) acquired from 23 CUD subjects and 23 matched controls while performing an n- back WM task, we conducted the DCM analysis with left (L) DLPFC, right (R) DLPFC, L VLPFC, R VLPFC, L caudate, and R caudate as the nodes. A survey (Bossong et al., 2014) of previous working memory studies suggests that cannabis-related negative effects on working memory could be in the encoding processes, which engage the L caudate rather than the R caudate (Chein and Fiez, 2001; Chang et al., 2007). Furthermore, CUD individuals show lower activation in the R DLPFC during WM tasks (Kanayama et al., 2004; Nestor et al., 2008; Schweinsburg et al., 2008b). Based on these rationales, our first specific hypothesis was that the CUD individuals would have smaller modulatory change in the R DLPFC to L caudate EC than the controls, reflecting a negative effect of chronic cannabis use. Previous studies found greater working memory activations in L DLPFC (Jager et al., 2010; Smith et al., 2010), R VLPFC (Kanayama et al., 2004; Smith et al., 2010), and L VLPFC (Jager et al., 2010). Thus, our second specific hypothesis was that the CUD individuals would have larger modulatory changes for other prefrontal to striatal ECs (originating from L DLPFC, L VLPFC, and R VLPFC) than the controls, reflecting a compensatory mechanism. Both caudate and putamen are active during working memory tasks (Wager and Smith, 2003). We specifically hypothesized changes in connectivity to the caudate, as opposed to other striatal structure (e.g., putamen, nucleus accumbens) because the caudate directly connects to DLPFC and

VLPFC (Yeterian and Pandya, 1991; Leh et al., 2007). A diffusion tractography study (Leh et al., 2007) indicated that the putamen does not directly connect to DLPFC or VLPFC although it directly connects to motor regions. Another study (Lucas-Neto et al., 2015) using diffusion tractography reported that the nucleus accumbens directly connects to frontal pole, orbitofrontal cortex, and anterior cingulate cortex rather than DLPFC and VLPFC.

The studies reviewed above investigated both adolescent and adult CUD individuals. The present study investigated adult CUD subjects, but some of them used cannabis during adolescence. Frontostriatal connectivity is thought to undergo normative maturation during adolescence (Paus, 2005; Hwang et al., 2010). Relative to adults, cannabis may exert greater negative effect on the brain of adolescents because cannabis could disrupt the ongoing neurodevelopment (Spear, 2000). Thus, varying age of CUD samples would be a factor underlying the experimental findings. Based on human (Ehrenreich et al., 1999; Huestegge et al., 2002; Fontes et al., 2011; Gruber et al. 2012; Solowij et al., 2012; Tamm et al., 2013) and animal (Schneider and Koch, 2003; O'Shea et al., 2004) studies indicating that altered brain functions are associated with early-onset of cannabis use, we conducted exploratory analyses to test above hypotheses in an early-onset subgroup of CUD vs. a late-onset subgroup of CUD.

2. Methods and materials

2.1. Participants

Data were obtained from the Human Connectome Project (HCP) (Van Essen et al. 2013). The experiments were performed in accordance with relevant guidelines and regulations and all experimental protocol was approved by the Institutional Review Board (IRB) (IRB # 201204036; Title: 'Mapping the Human Connectome: Structure, Function, and Heritability'). Written informed consent was obtained from all participants. Our data analysis was performed in accordance with ethical guidelines of the Virginia Commonwealth University.

The subject inclusion criteria were: (I) right-handed; (II) lifetime cannabis dependence (for CUD subjects) as defined by the Self-Reported Substance Use and Abuse measures from Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994); and (III) positive urine test for delta-9-tetrahydrocannabinol (THC) (for CUD subjects). The positive THC result and other drug use measures are based on the data and HCP Data Dictionary released by HCP (https://db.humanconnectome.org/data/projects/HCP_1200). Information regarding the device and THC threshold used for the urine test is not directly available to the authors of this manuscript. The exclusion criteria were: (I) higher than moderate level of nicotine dependence as determined by the scoring on the Fagerstrom Test for Nicotine Dependence (Kozlowski et al., 1994); (II) breath alcohol concentration greater than 0.05 g/210 L; (III) positive urine test for cocaine, opiates, and drugs other than cannabis; and (IV) meeting DSM-IV (American Psychiatric Association, 2000) criteria of alcohol dependence. Based on the inclusion/exclusion criteria, 23 CUD subjects and 676 potential non-drug-using subjects were identified from 900 participants. Twenty-three non-drug-using controls were then selected from 676 non-drug-using subjects in order to match the 23 CUD subjects, in sex, age, education, alcohol use, tobacco use, and self-reported lifetime use of other non-

cannabis drugs. Specifically, one control subject was selected to match one CUD subject, with sex as the first priority, age, and education as the second priority, and alcohol use, tobacco use, and self-reported lifetime use of other non-cannabis drugs as the third priority in matching. See Table 1 for the demographic information of both groups. The two groups were not significantly different in age ($t=0.4708$, degrees of freedom [df]=44, $p=0.6401$), sex (Fisher's exact test $p=1$, two-tail), education ($t=0$, df = 44, $p=1$), alcohol use ($t=0.2497$, df = 44, $p=0.8040$), tobacco use ($t=0.5144$, df = 44, $p=0.6096$), and self-reported lifetime use on more than 10 occasions of any non-cannabis drug (Fisher's exact test $p>0.1868$, two-tail). The age of 17 years was used as the threshold of early-onset (Solowij and Battisti, 2008). Based on this threshold, 16 CUD individuals belonged to the early-onset CUD subgroup (11 males, 6 females, 28.4 ± 3.4 years old, 15.0 ± 1.7 years of education) and the 7 remaining CUD individuals belonged to the late-onset CUD subgroup (6 males, 1 female, 27.6 ± 4.0 years old, 13.6 ± 1.7 years of education). The two CUD subgroups showed a trend significant difference in education ($t=1.8389$, df = 21, $p=0.0801$), no significant difference in alcohol use ($t=0.1417$, df=21, $p=0.8887$), and no significant difference in tobacco use ($t=0.5923$, df = 21, $p=0.5923$).

2.2. In-scanner working memory task

The HCP n-back working memory task (Barch et al., 2013) used pictures of faces, places, tools and body parts as the stimuli to assess WM. Two n-back fMRI runs were conducted. Each run consists of four “2-back” task blocks (10 trials of 2.5 s each per block, block duration = 25 s), four “0-back” task blocks (10 trials of 2.5 s each per block, block duration = 25 s) and four fixation blocks (block duration = 15 s). All the stimulus types were used in each task type, but the order of stimulus types was random. A 2.5 s cue indicated the task type (and target for 0-back) at the start of the block. On each trial, the stimulus was presented for 2 s, followed by a 500 ms inter-trial-interval. Two or three trials in each task block presented non-target lures.

2.3. Out-scanner tasks testing executive function/working memory

2.3.1. Dimensional change card sort—HCP used dimensional change card task (about 4 min) to measure executive function/cognitive flexibility. Two target pictures were presented that vary along two dimensions (e.g., shape and color). Participants were asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). Some “Switch” trials, in which the participant must change the dimension being matched, were used in order to test cognitive flexibility. Scoring was based on a combination of accuracy and reaction time.

2.3.2. Flanker task—HCP used the Flanker task (about 3 min) to jointly measure attention and inhibitory control. During the test, the participant was requested to focus on a given stimulus while inhibiting attention to stimuli (arrows) flanking it. Sometimes the middle stimulus is pointing in the same direction as the “flankers” (congruent) and sometimes in the opposite direction (incongruent). Scoring was based on a combination of accuracy and reaction time.

2.3.3. List sorting—HCP used the list sorting task to assess working memory. With two different conditions (1-List and 2-List), this task requires the participant to sequence different visually- and orally-presented stimuli. Pictures of different foods and animals were displayed with both a sound clip and written text that name the item. In the 1-List condition, participants were required to order a series of objects (either food or animals) in size order from smallest to largest. In the 2-List condition, participants were presented both food and animals and are asked to report the food in size order, followed by the animals in size order.

2.4. fMRI data acquisition

As described in Barch et al. (2013), whole-brain echo-planar imaging acquisitions were acquired with a 32-channel head coil on a modified 3 T Siemens Skyra scanner (Erlangen, Germany), with repetition time = 720 ms, echo time = 33.1 ms, flip angle = 52°, band- width = 2290 Hz/pixel, in-plane field-of-view = 208 mm × 180 mm, 72 slices, 2.0 mm isotropic voxels, multi-band acceleration factor of 8. Two fMRI runs, with left-to-right and right-to-left phase encodings, respectively, were acquired, preprocessed and concatenated for DCM analysis.

2.5. fMRI preprocessing

Per Glasser et al. (2013), fMRI data were “minimally” preprocessed to implement gradient unwarping, motion correction, fieldmap-based EPI distortion correction, brain-boundary-based registration of EPI to structural T1-weighted scan, non-linear registration into standard MNI152 space, and grand-mean intensity normalization (Functional Pipelines v3.4.0; v3.12.0; v3.13.2). The voxel size of the minimally- processed data is $[2 \times 2 \times 2]$ mm.

Twelve head motion correction parameters were released by HCP (Glasser et al., 2013). See Table 2 for the detailed information of these parameters for both groups. For each fMRI run, we quantified these head motion parameters using cumulative value (Haller et al., 2014) and maximal value. For each motion parameter, the corresponding cumulative value and maximal value were computed as the summation and the maximum respectively, of the absolute values of this motion parameter across the entire run. For each subject, the cumulative value and maximal value were computed as the mean and the maximum respectively, across the left-to-right phase-encoding fMRI run and right- to-left phase encoding fMRI run. As shown in Table 2, none of the differences between groups for the cumulative head motion value was statistically significant after Bonferroni correction (corrected $p > 0.95$). In addition, none of the differences between groups for the maximal head motion value was statistically significant after Bonferroni correction (corrected $p > 0.35$).

Following Hillebrandt et al. (2014), an additional step of pre- processing was performed on the minimally-processed fMRI data: spatial smoothing with a 4-mm Gaussian kernel, using Statistical Para- metric Mapping 12 (SPM12) software (<http://www.fil.ion.ucl.ac.uk/spm/>).

2.6. SPM univariate analysis of contrast activation

The nodes of DCM were selected based on brain activation elicited by the working memory task, as revealed by SPM univariate analysis of contrast activation. In the first-level

univariate statistical analysis, the two preprocessed fMRI runs were included in the model as two sessions. The 2-back and 0-back blocks were modeled by boxcar functions convolved with the SPM12 canonical hemodynamic response function. The parameters for each task condition were estimated using the General Linear Model (Friston, 1995) without global normalization. Following Barch et al. (2013), the fMRI data was high-pass filtered with a cut-off period of 200 s. Activation was defined as the contrast of 2-back –(minus) 0-back parameter estimate.

In order to determine between-group differences in regional activation, an SPM12 second-level two-sample t-test was conducted voxel- wise for the 2-back–0-back contrast image. Statistical significance was defined as family-wise error corrected cluster probability (p) < (less than) 0.05 (two-tail).

An SPM12 second-level one-sample t-test was conducted to determine the DCM nodes, which were selected based on the regions that activated across both groups combined (Seghier et al., 2010). Uncorrected cluster $p < 0.05$ (two-tail), which is commonly accepted (Friston et al., 2003) for DCM node selection, was used as the activation threshold to define nodes for DCM analysis.

For all second-level analyses, the cluster-defining threshold was $t = 2.4$. Anatomical labels for regions of activation were determined using the Anatomical Automatic Labeling2 (AAL2) toolbox (Rolls et al., 2015).

2.7. Dynamic causal modeling

fMRI-based DCM is a biophysical model of how the underlying neuronal connectivity generates the observed fMRI signal (Friston et al., 2003). DCM has been described elsewhere (Friston et al., 2003; Ma et al., 2012; 2014). In brief, DCM is a system of bilinear differential state equations with coefficients (in units of Hz) (Friston et al., 2003). A node in the model that receives driving inputs is the brain region which first experiences a change in neuronal activity. This node then influences other nodes. The endogenous connectivity measures the EC strengths between nodes, regardless of the moment-to-moment switching on and off of inputs. In other words, endogenous connectivity is the overall default directionality and strength of connectivity irrespective of momentary task condition. Experimental conditions can modulate the endogenous connectivities. Their modulation effects quantify increased or decreased connectivity strength compared to the endogenous connectivity.

Following Hillebrandt et al. (2014), two new experimental conditions called “All-back” and “2-back – (minus) 0-back” were created using appropriate parametric regressors as described in Buchel et al. (1998). The “All-back” condition, which reflects the combined effect of the 2-back and 0-back stimuli, was used as a single input to the DCM. The 2-back–0-back condition, which reflects the special effect of 2-back over 0-back (i.e., increased WM demand), was used as a putative modulator of EC. In this study, the change in EC corresponding to the 2-back – 0-back modulator is termed as modulatory change.

2.7.1. DCM nodes—Following the procedures by Ma et al. (2012; 2014), the DCM nodes (regions) were chosen based on simultaneously meeting all of the following criteria: (I) show activation ($p < 0.05$ two-tail at uncorrected cluster level) in the SPM second-level analysis of the combined groups; (II) activate consistently during WM tasks in previous studies (Wager and Smith, 2003; Owen et al., 2005); (III) belong to visual and spatial cortico-striatal circuits (Lawrence et al., 1998); and (IV) belong to aberrant neurocircuits thought to underlie substance use disorders (Bechara, 2005; Bickel et al., 2007; Everitt et al., 2008; Koob and Volkow, 2016). Based on these criteria, the following six nodes were selected as DCM nodes: (1) L DLPFC; (2) R DLPFC; (3) L VLPFC (including inferior frontal gyrus pars opercularis, pars triangularis, and pars orbitalis); (4) R VLPFC; (5) L caudate; and (6) R caudate. The posterior parietal cortex was not included as a DCM node because this study chose to focus on fronto-striatal connectivity (see the Discussion section for expanded discussions).

The regional activation corresponding to each node was obtained based on the set-theoretic intersection of the corresponding atlas-based binary mask and the activation clusters that were determined by the SPM second-level one-sample t-test. The atlas-derived binary masks for all brain regions were obtained from the AAL2 atlas. The binary mask for DLPFC was based on the binary mask of middle frontal gyrus (MFG), which was further constrained by the conservative bounding box (Brodmann Areas 46 and 9) defined in (Rajkowska and Goldman-Rakic, 1995). The regional fMRI activations were constrained by these binary masks, and the local maximum within each activation cluster was obtained. The nodes of DCM were defined as spheres (see Fig. 1 for the location) centered at the local maximum within each regional activation. The radius for prefrontal nodes was 5 mm, and the radius for the caudate nodes was 3 mm. Smaller spheres were used as the caudate nodes because the regional activations in these regions were relatively smaller. The same nodes were used for each subject.

The fMRI time series of each node, i.e., the blood-oxygen-level dependent (BOLD) signal over time in that node, was extracted by using the principal-eigenvariate of that node (Ma et al., 2014). Each time series was also adjusted by the F-contrast of the effects-of-interest (Stephan et al., 2010).

2.7.2. DCM parametric empirical Bayes (PEB) analysis—The PEB approach (Friston et al., 2016), as implemented in SPM12 (Revision 6906), was used to evaluate group differences in the DCM parameters. PEB allows to empirically update priors for each subject during the DCM analysis. The method of conducting PEB analysis can be found online (<https://en.wikibooks.org/wiki/User:Peterz/sandbox>). In brief, the analysis started from specifying an initial putative “full” model, which was related to the driving input (All-back stimuli) and the 2-back–0-back modulator defined above. The term “full” is used here in the sense that (1) the putative driving input entered all of the six nodes; (2) each node was putatively interconnected to all other nodes, and (3) the 2-back – 0-back modulator putatively modulated all of the 30 interconnectivities between nodes. Then, all full models (one per subject) were assembled into a cell array with one subject per row and one DCM per column. These models, as organized by the cell array, were estimated using the SPM12 code (spm_dcm_peg_fit.m), which facilitates drawing subjects out of local optima towards

the group mean (<https://en.wikibooks.org/wiki/User:Peterz/sandbox>). Next, a second level (group) GLM and a design matrix (ones “1” for CUD subjects and negative ones “-1” for controls) were specified, with alcohol and tobacco use as the covariates (Table 1). Based on the GLM, design matrix, and the estimated full models, the second level (group) PEB model was estimated using the SPM12 code (spm_dcm_peb.m). The estimated PEB model contains all parameters representing group effects on each DCM parameter. After that, between-group effects were identified using the SPM12 code (spm_dcm_peb_bmc.m), which prunes away any parameters from the PEB model that do not contribute to the model evidence.

2.8. Statistical analysis

Student’s t-test was used to evaluate group differences on continuous variables (e.g., age). Fisher’s exact test was used to evaluate group differences on categorical variables (e.g., sex). An analysis of variance (ANOVA) was used to analyze behavioral performance, with group (CUD and Control) as the between-subjects factor, and working memory level (2-back and 0-back) as the within-subjects factor. Spearman partial correlation (with alcohol use and tobacco use as covariates) was used for the correlation analysis.

3. Results

3.1. Behavioral performance

3.1.1. In-scanner performance—The mean and standard deviation of the reaction time (RT) and the number of correct responses (NCR) during 2-back and 0-back blocks (in scanner) are shown in Table 3, for the two groups. An ANOVA on RT showed that the main effect of group ($F = 0.3800$; $df = 1,91$; $p = 0.5386$) and the interaction between group and n-back level ($F = 0.3100$; $df = 1,91$; $p = 0.5777$) were not significant. The main effect of n-back level was significant ($F = 47.0800$; $df = 1,91$; $p < 0.0001$), with longer RT during 2-back than 0-back. Another ANOVA on the NCR showed no main effect of group ($F = 0.6900$; $df = 1,91$; $p = 0.4079$) nor group $\times$ EC interaction effect ($F = 0.9800$; $df = 1,91$; $p = 0.3237$). As with RT, the main effect of n-back level on NCR was significant ($F = 6.3600$; $df = 1,91$; $p = 0.0135$), with greater correct responses during 0-back than 2-back.

Corresponding to the definition of the modulatory change (the change in EC corresponding to the 2-back – 0-back modulator), two relative behavioral performance measures were defined: $RT = RT(2\text{-back}) - RT(0\text{-back})$, and $NCR = NCR(2\text{-back}) - NCR(0\text{-back})$. The mean and standard deviation of RT and NCR are shown in Table 3 for the two groups. There was no significant group difference in both RT ($t = 0.9505$, $df = 44$, $p = 0.3470$) and NCR ($t = 1.5838$, $df = 44$, $p = 0.1204$).

3.1.2. Out-scanner performance—The mean and standard deviation of the behavioral performance of the three out-scanner tasks (card sorting, Flanker, and list sorting) are shown in Table 3, for the two groups. There was no significant group difference in the performance of the dimensional change card sort task ($t = 0.3617$, $df = 44$, $p = 0.7193$), the Flanker task ($t = -1.6349$, $df = 44$, $p = 0.1092$), and the list sorting task ($t = -0.6151$, $df = 44$, $p = 0.5416$).

3.2. SPM univariate analysis of contrast activation

There was no statistically significant group difference in regional brain activation for the contrast of 2-back minus 0-back. Additional SPM analyses testing group activation differences in 2-back or 0-back conditions alone (i.e. relative to the implicit baseline/fixation) did not find significant group difference in either 2-back alone or 0-back alone. Across both groups combined, there were several clusters for the contrast of 2-back–0-back with the cluster level $p < 0.05$ (uncorrected, two-tail). See Table 4 for the detailed information regarding these clusters, i.e., AAL2 label, and number of voxels, maximal t value, and Montreal Neurological Institute (MNI) coordinates of each labeled region. These clusters, as shown in Fig. 2, were used to select the DCM nodes.

3.3. DCM effective connectivity analysis

3.3.1. Group difference in ECs—For the comparison between the CUD group and the Control group (CUD minus Controls), the mean (Hz) and posterior probability (PP) of the difference in the modulatory changes are shown in Table 5 (0 $\leq$ PP $\leq$ 1.00), as well as the mean of the modulatory changes (averaged between CUD group and Control group. In Bayesian analysis, the PP is the posterior probability that a parameter should be included in the model given the available information (such as data, priors, and so on). Thus, the higher the PP, the greater the probability for inclusion in the model. The cut off of PP for the statistical inference is arbitrary. In this study, we chose a cut off of 0.95 (or 95%). This would mean that the probability is at least 95% that a DCM parameter (the modulatory change here) is different from zero. Given the cut off PP (0.95) that we had set, the modulatory changes with PP lower than 0.95 were considered non-significant in this study, such as the difference in the EC L DLPFC to R caudate EC (PP = 0.6468).

Among the six prefrontal-striatal effective connectivities in the model, four of them showed reliable group difference (PP = 1.00), i.e., R DLPFC to L caudate, L DLPFC to L caudate, R DLPFC to R caudate, and R VLPFC to L caudate ECs (Fig. 3). Compared to the controls, the CUD group showed smaller modulatory change for the R DLPFC to L caudate EC (group difference = -0.2260 Hz); and greater modulatory changes for the L DLPFC to L caudate (group difference = 0.2405 Hz), R DLPFC to R caudate (group difference = 0.2664 Hz), and R VLPFC to L caudate (group difference = 0.1652 Hz) ECs.

3.3.2. ANOVA analysis testing Group $\times$ Pathway interaction effect—If the smaller modulatory change in EC for the R DLPFC to L caudate pathway reflects the negative effects of chronic cannabis use, and the greater modulatory change in EC for the L DLPFC to L caudate pathway reflects a compensatory mechanism, the modulatory changes for these pathways should show opposite patterns between the two groups. In order to test this, we conducted ANOVA with the modulatory change in EC as the dependent variable, Group (2 levels: CUD and Control) and Pathway (2 levels: R DLPFC to L caudate, and L DLPFC to L caudate) as the independent variables, and Group $\times$ Pathway as the interaction effect. The detailed results of the ANOVA analysis are shown in Table 6 and Fig. 4. A significant Group $\times$ Pathway interaction effect was found (Bonferroni corrected $p < 0.0003$). Because of the significant interaction effect, we conducted a post-hoc analysis investigating the simple main effects within each pathway separately. The modulatory change in EC was

significantly smaller (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the R DLPFC to L caudate pathway, but significantly greater (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the L DLPFC to L caudate pathway.

Two other ANOVAs (#2 and #3) were conducted, which were similar to the above ANOVA model, except that the Pathway variable consisted of R DLPFC to L caudate, and L DLPFC to L caudate, for ANOVA #2, and the Pathway variable consisted of R DLPFC to L caudate, and R VLPFC to L caudate, for ANOVA #3. The detailed results of ANOVA #2 are shown in Table 6 and Fig. 5. A significant Group $\times$ Pathway interaction effect was found (Bonferroni corrected $p < 0.0003$). The analysis of simple main effects showed that the modulatory change in EC was significantly smaller (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the R DLPFC to L caudate pathway, but significantly greater (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the R DLPFC to R caudate pathway.

The detailed results of ANOVA #3 are shown in Table 6 and Fig. 6. A significant Group $\times$ Pathway interaction effect was found (Bonferroni corrected $p < 0.0003$). The analysis of simple main effects showed that the modulatory change in EC was significantly smaller (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the R DLPFC to L caudate pathway, but significantly greater (Bonferroni corrected two-tail $p < 0.05$) in the CUD group than controls for the R VLPFC to L caudate pathway.

3.3.3. Exploratory analyses—For the comparison between the early-onset CUD subgroup and the late-onset CUD subgroup (early-onset CUD minus late-onset CUD), the mean and PP of the difference in the modulatory changes are shown in Table 5. Only three ECs showed reliable difference (PP = 1.00) between the two subgroups: relative to the late-onset subgroup, the early-onset subgroup showed greater modulatory changes in the L DLPFC to R DLPFC (subgroup difference = 0.2435 Hz) and L DLPFC to R caudate (subgroup difference = 0.1909 Hz) ECs, and smaller modulatory change in L VLPFC to R DLPFC (subgroup difference = -0.3758 Hz) EC. The early-onset subgroup showed a tendency ($0.74 < PP < 0.79$) for smaller modulatory changes than the late-onset subgroup in L VLPFC to R VLPFC (-0.1101 Hz), L VLPFC to L caudate (-0.1505 Hz), L VLPFC to R caudate (-0.1415 Hz) ECs.

3.4. Relationship between connectivity and behavioral performance

Spearman partial correlation analysis (with alcohol use and tobacco use as covariates) was conducted in order to test the relationship between each of the behavioral performances (RT, PCT, card sorting, Flanker, and list sorting as shown in Table 3) and each of the four prefrontal-striatal effective connectivities showing reliable group differences reported above, in the CUD group as a whole, early-onset CUD subgroup, late-onset CUD subgroup, and the Control group respectively.

There was a significant positive partial correlation between the behavioral performance on the Flanker task and the modulatory change of the R DLPFC to R caudate EC within the CUD group ($\rho = 0.6723$, uncorrected $p = 0.0008$, Bonferroni corrected $p = 0.0252$).

However, without covarying alcohol and tobacco use, the full correlation became non-significant ($\rho = 0.2231$, uncorrected $p = 0.3182$). The scatter plot showing the relationship between the behavioral performance of the Flanker task and the modulatory change of the R DLPFC to R caudate EC is shown in Fig. 7, for all the CUD subjects. No significant or marginally significant correlation was found for the other correlation analyses (uncorrected $p > 0.05$).

4. Discussion

We evaluated WM function in CUD subjects at the neurocircuit EC level as well as the behavior level. Relative to the control group, the CUD group showed (1) similar behavioral performance; (2) smaller modulatory change in the R DLPFC to L caudate EC; and (3) greater modulatory changes in the L DLPFC to L caudate, R DLPFC to R caudate, and R VLPFC to L caudate ECs.

Consistent with previous WM studies (Kanayama et al., 2004; Schweinsburg et al., 2005; Jager et al., 2006; Padula et al., 2007; Nestor et al., 2008; Schweinsburg et al., 2008a; 2008b; Smith et al., 2010; Schweinsburg et al., 2010; Cousijn et al., 2014a; Cousijn et al., 2014b), no group difference was found in the behavioral performance during the working memory task. This consistent finding of normal behavioral performance in the CUD individuals is the basis of a hypothesized compensatory mechanism. No group difference was found in the regional contrast-elicited brain activation either. This is perhaps because substance abuse treatment history was exclusionary for the HCP criteria, and thus the CUD individuals used in the present study may have been less likely to be heavy users. Even if there is no statistically significant group difference in regional brain activation, it is possible that there exist group differences in connectivity measures (Rowe, 2010), such as in the present study. In fact, it has been suggested that DCM nodes for between-group comparisons should be selected in general from brain regions that do not show a group difference in regional activation (Seghier et al., 2010). This is to ensure that the models are comparable between groups. As suggested by Seghier et al. (2010), the group differences should be fully characterized by reporting both group difference in BOLD activation and group difference in connectivity. In general, however, it was suggested that the DCM nodes should not be selected from the areas showing group difference in BOLD activation in order to avoid the effects on the connectivity results exerted by the group difference in BOLD activation (Seghier et al., 2010). Given the group difference in EC and the lack of group difference in regional brain activation, future studies are warranted to examine this discrepancy in more detail.

Consistent with the previous studies (Kanayama et al., 2004; Nestor et al., 2008; Schweinsburg et al., 2008b) that show less WM activation in right DLPFC in CUD individuals, the CUD group showed smaller modulatory change for the R DLPFC to L caudate EC than the Control group, implying that the R DLPFC to L caudate EC was less functional in the CUD group than the Control group. Given that previous studies (Chein and Fiez, 2001; Chang et al., 2007) showed that the L caudate (rather than R caudate) is responsible for encoding, the DCM finding of reduced R DLPFC to L caudate EC suggests a possible cannabis-related negative effect on encoding during WM (Bossong et al., 2014), or

on the other hand may suggest a negative effect on encoding that may have been contributory to the development of frequent cannabis use. In addition, smaller EC from L DLPFC to L striatum has been observed in individuals with cocaine use disorder during a working memory task (Ma et al., 2014). The between-study difference in the laterality of DLPFC could be related to the task stimuli: digital sequences were used in Ma et al. (2014), and pictures were used in the present study. Thus it appears that there are changes in DLPFC to L caudate ECs in CUD and cocaine use disorder, consistent with the dual-system theory for SUDs (Bechara, 2005; Bickel et al., 2007; Everitt et al., 2008).

In addition to the normal behavioral performance and the smaller modulatory change in the R DLPFC to L caudate EC, the CUD group showed greater modulatory changes by WM demand in the R DLPFC to R caudate, L DLPFC to L caudate, and R VLPFC to L caudate ECs. Consistent with previous studies showing greater WM activation in R DLPFC (Jager et al., 2010; Smith et al., 2010), R VLPFC (Kanayama et al., 2004; Smith et al., 2010), and L VLPFC (Jager et al., 2010) in CUD, the present results suggest that more control must be exerted from prefrontal regions over the striatal regions in order to achieve normal behavioral performance in CUD. The significant group $\times$ pathway interaction effects on the modulatory change (Table 6, Figs. 4–6) suggest that the CUD individuals who had smaller modulatory change in EC for the R DLPFC to L caudate pathway, also had greater modulatory changes in EC for the R DLPFC to R caudate, L DLPFC to L caudate, R VLPFC to L caudate pathways. These results are consistent with the hypothesized compensatory mechanism in the CUD individuals. The interpretation that the R VLPFC to L caudate increase in EC is compensatory for the R DLPFC to L caudate decrease in EC is consistent with previous studies showing the compensatory role of the VLPFC for DLPFC function (see Tan et al., 2007 for review). However, none of these modulatory changes showed significant correlation with the behavioral performance, except there was a significant positive partial correlation between the behavioral performance on the Flanker task and the modulatory change of the R DLPFC to R caudate EC within the CUD group. However, without covarying alcohol and tobacco use, the full correlation was non-significant. These non-significant correlations suggest that in the present study, the behavioral performance may not be dependent on a single connectivity. Most likely, the behavioral performance depends on the overall network. Future work could utilize multivariate data analysis (Habeck et al., 2010) to test whether connectivity changes across a full network explain behavior variability. Alternatively, the greater modulatory changes may reflect other cognitive processes. However, the present study does not provide direct evidence about this alternate possibility. While the laterality of the prefrontal compensatory mechanism is controversial (Holler- Wallscheid et al., 2017), our DCM findings indicated that the increase in L DLPFC to L caudate and R DLPFC to R caudate ECs could represent a bilateral compensatory mechanism.

In order to investigate the effect of early-onset of cannabis use, we conducted an exploratory analysis by comparing the ECs between the early-onset CUD subgroup and the late-onset CUD subgroup. Relative to the late-onset CUD subgroup, the early-onset CUD subgroup had smaller modulatory changes for the L VLPFC to L caudate and L VLPFC to R caudate prefrontal-striatum pathways. Although the findings are preliminary ($n = 7$ for the late-onset CUD subgroup, $0.74 < PP < 0.79$), the result of this exploratory analysis, if confirmed by a

larger study, would suggest a possible negative effect of the early use of cannabis to result in greater compensatory EC, consistent with previous studies regarding the effects of early-onset use (Ehrenreich et al., 1999; Huestegge et al., 2002; Fontes et al., 2011; Gruber et al., 2012; Solowij et al., 2012; Tamm et al., 2013).

It is possible that the observed R DLPFC to L caudate EC alteration in CUD could be related to altered neurotransmitter functions (Auclair et al., 2000; Bossong et al., 2009; Hirvonen et al., 2012). The DLPFC and caudate both have high densities of cannabinoid type 1 receptors (Freund et al., 2003). THC, the major psychoactive chemical in cannabis, modulates the prefrontal-striatal networks by affecting prefrontal cortical and striatal dopamine and glutamate transmission (see Pattij et al. [2008] for review). In rodents, there is evidence that THC specifically counteracts cortical-dorsal striatal transmission (Gerdeman and Lovinger, 2001; Orru et al., 2011; Justinova et al., 2013). However, it is still unclear what are the factors underlying the selective changes of the prefrontal-striatal ECs. Altered brain perfusion (Herning et al., 2001), white matter integrity (Rapp et al., 2012), or gray matter structure (Koenders et al., 2016) are other potential underlying factors.

Head motion is very common in fMRI studies, in particular in the studies of neuronal disorders (Ikari et al., 2012). HCP took several measures in order to address head motion (Marcus et al., 2013). Given the HCP fMRI voxel size ($2 \times 2 \times 2$ mm), it is a common practice to set 2 mm (in each of x, y, z translations) and 2° (in each of the x, y, z rotations) as the exclusion criteria (Wylie et al., 2014; Couvy-Duchesne et al., 2016). Thus, the maximal head motions (1.01 ± 0.98 mm in z translation and 1.41 ± 1.39 degree in x rotation, Table 2) suggest that fMRI scans used in this study were of high quality in terms of head motion. Furthermore, there were no statistically significant differences between groups for cumulative head motion (corrected $p > 0.95$) or maximal head motion (corrected $p > 0.35$).

The strengths of the present study are the use of the novel DCM PEB method, which allows the updating of priors for each subject during the DCM analysis, and the evaluation of the relative effects of the 2-back condition over the 0-back condition on the ECs. However, this study also has several limitations. Firstly, a limited number of nodes are allowed in DCM analysis. It is possible that other neural interconnectivities are also important for WM but were not identified because the connecting regions were not included as nodes (such as posterior parietal cortex and anterior cingulate cortex) in the DCM analysis. One reason for the exclusion of potential nodes is study feasibility. With the increase in the number of nodes, the time needed for the DCM analysis increases quadratically (Seghier and Friston, 2013). Although it has been demonstrated that DCM for resting state fMRI is relatively computationally efficient and facilitates to analysis resting state networks with over 30 nodes (Razi et al., 2017), it is still not feasible to conduct such large scale DCM analysis for task-based fMRI. Thus, strict node selection criteria were used in the present study to control the number of nodes. Posterior parietal cortex was not included because this study chose to focus on frontostriatal connectivity. Connectivity in other WM networks may have divergent associations. This is particularly true for posterior parietal cortex which has been associated with early cannabis onset (Becker et al., 2010) and particularly with WM encoding in cannabis onset associations (Tervo-Clemmens et al., 2018). Anterior cingulate cortex was not included because it does not directly belong to the visual and spatial cortico-

striatal circuits (Lawrence et al., 1998). Secondly, the exploratory analysis (i.e., early-onset subgroup of CUD vs. late-onset subgroup of CUD) is associated with biased gender distribution (only one female in the late-onset subgroup), and small sample size ($n = 16$ for the early-onset subgroup, and $n = 7$ for the late-onset subgroup), which considerably reduced power. Thus, the results of this exploratory analysis (i.e., early-onset subgroup of CUD vs. late-onset subgroup of CUD) should be interpreted cautiously and regarded as preliminary. Including the age of onset as a continuous variable in a regression analysis may be more appropriate because it takes advantage of the entire sample of CUD subjects. However, such an analysis cannot be conducted because the exact age of onset was not released by the HCP. Only category variable is available (1, 2, 3, and 4 represents age of onset 14 years, between 15 and 17 years, between 18 and 20 years, and 21 years, respectively). Thirdly, all the included CUD individuals had positive THC urine testing result. Therefore potential acute and residual effects of the drug itself cannot be ruled out. Finally, the WM task paradigm used by HCP was a block design; thus we cannot distinguish the specific WM component processes that were involved (e.g., encoding).

In spite of these limitations, the DCM analysis revealed that during the n-back WM task, the CUD group showed a smaller modulatory change in the R DLPFC to L caudate EC, and greater modulatory changes in the L DLPFC to L caudate, L DLPFC to L caudate, and L DLPFC to L caudate ECs relative to controls. The smaller modulatory change in the R DLPFC to L caudate EC could reflect a negative effect of chronic cannabis use on encoding and supports the dual-system SUD theory addressing the imbalanced interaction between the reflective prefrontal system and the impulsive striatal system. The greater modulatory changes in the L DLPFC to L caudate, L DLPFC to L caudate, and L DLPFC to L caudate ECs could reflect a compensatory mechanism to achieve normal performance.

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Fig. 1. Location of all spherical VOIs used as node in the DCM analysis, visualized with the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (Xia et al., 2013). The MNI coordinates (mm) and color codes for these VOIs were: L DLPFC (−32, 34, 34; blue color), R DLPFC (33, 38, 32; blue color), L VLPFC (−49, 17, 4; green color), R VLPFC (53, 13, 15; green color), L caudate (−16, 5, 18; red color), R caudate (16, 4, 19; green color). L = left. R = right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

The clusters found by the SPM12 second-level random effects one-sample t-test analysis, across both groups combined, for the contrast of 2-back–0-back with the cluster level $p < 0.05$ (uncorrected, two-tail).

Fig. 3.

Schematic diagram representing group difference (CUD minus Control) in modulatory change in the prefrontal-striatal effective connectivities by WM demands. The endogenous connectivities are denoted by line with arrow. The modulatory changes are depicted by dash lines ending with solid dot. L = left. R = right.

Fig. 4. Interaction effect between group (Control and CUD) and pathway (R DLPFC to L caudate, and L DLPFC to L caudate) on the modulatory change in EC (Hz).

Fig. 5. Interaction effect between group (Control and CUD) and pathway (R DLPFC to L caudate, and R DLPFC to R caudate) on the modulatory change in EC (Hz).

Fig. 6. Interaction effect between group (Control and CUD) and pathway (R DLPFC to L caudate, and R VLPFC to L caudate) on the modulatory change in EC (Hz).

Fig. 7. Scatter plot between the performance of the Flanker task and the modulatory change of R DLPFC to R caudate effective connectivity (Hz) in all the CUD subjects.

Table 1

Demographic information of the CUD and control groups. F = female, M = male, L = left, R = and right.

Parameter	CUD (<i>n</i> = 23)	Control (<i>n</i> = 23)
Age [years] mean and standard deviation (range)	28.2 ± 3.5 (22–33)	28.7 ± 3.7 (22–35)
Sex	6 F, 17 M	7 F, 16 M
Handedness	23 R, 0 L	23 R, 0 L
Education [years] mean and standard deviation (range)	14.6 ± 1.8 (11–17)	14.6 ± 2.1 (11–17)
Total number of alcohol drinks in the past 7 days (range)	8.1 ± 8.2 (0–25)	7.5 ± 8.1 (0–25)
Total number of any tobacco used in the past 7 days (range)	22.9 ± 27.4 (0–75)	18.9 ± 25.3 (0–70)
Number of subjects used cocaine more than 10 times	5	2
Number of subjects used illicit drugs more than 10 times	3	1
Number of subjects used hallucinogens more than 10 times	5	1
Number of subjects used opiates more than 10 times	5	1
Number of subjects used sedatives more than 10 times	5	1
Number of subjects used stimulants more than 10 times	5	1
Number of subjects with 1st marijuana use earlier than 17 years old	16	N/A

Table 2

Mean and standard deviation of 12 motion correction parameters, for the two subject groups. The mean and the standard deviation were quantified in terms of cumulative value (see the text) and the maximal value (see the text). Student t-test was used to test group difference in each of the 12 parameters. For each test, the degree of freedom was 44. All the p values were Bonferroni corrected (uncorrected $p \times 12$). D = derivative.

Motion parameter	Cumulative		Statistics	Maximal		Statistics
	CUD	Control		CUD	Control	
x translation (mm)	51.1 ± 32.3	65.6 ± 51.8	$t = -1.13; p = 1$	0.44 ± 0.29	0.44 ± 0.25	$t = 0.02; p = 1$
y translation (mm)	89.5 ± 58.1	62.8 ± 39.8	$t = 1.82; p = 0.96$	0.59 ± 0.66	0.32 ± 0.16	$t = 1.90; p = 0.72$
z translation (mm)	144.4 ± 123.0	108.3 ± 63.0	$t = 1.26; p = 1$	1.01 ± 0.98	0.74 ± 0.40	$t = 1.23; p = 1$
x rotation (degree)	155.9 ± 118.6	143.4 ± 119.8	$t = 0.35; p = 1$	1.41 ± 1.39	0.93 ± 0.66	$t = 1.49; p = 1$
y rotation (degree)	61.6 ± 38.9	65.3 ± 48.5	$t = -0.28; p = 1$	0.44 ± 0.25	0.40 ± 0.23	$t = 0.54; p = 1$
z rotation (degree)	61.8 ± 43.7	71.8 ± 69.3	$t = -0.59; p = 1$	0.43 ± 0.23	0.43 ± 0.29	$t = -0.02; p = 1$
D x translation	24.2 ± 14.0	26.1 ± 13.3	$t = -0.48; p = 1$	0.33 ± 0.29	0.25 ± 0.12	$t = 1.25; p = 1$
D y translation	5.0 ± 2.6	5.0 ± 1.4	$t = -0.01; p = 1$	0.26 ± 0.36	0.11 ± 0.07	$t = 1.95; p = 0.72$
D z translation	12.9 ± 6.4	11.9 ± 5.8	$t = 0.52; p = 1$	0.51 ± 0.59	0.29 ± 0.33	$t = 1.55; p = 1$
D x rotation	10.8 ± 4.8	10.2 ± 3.9	$t = 0.42; p = 1$	0.91 ± 1.25	0.36 ± 0.31	$t = 2.04; p = 0.60$
D y rotation	7.6 ± 2.5	7.7 ± 2.0	$t = -0.17; p = 1$	0.22 ± 0.20	0.13 ± 0.06	$t = 2.24; p = 0.36$
D z rotation	6.7 ± 2.7	6.9 ± 2.8	$t = -0.18; p = 1$	0.23 ± 0.24	0.14 ± 0.06	$t = 1.86; p = 0.84$

Table 3

Mean and standard deviation of the in-scanner behavioral performance (RT, NCR, RT, and NCR of the n-back task) and the out-scanner behavioral performance (card sorting, Flanker, and list sorting tasks), in each subject group. The unit of RT and RT is ms. The summation of the number of correct responses and the number of incorrect responses are 40 for both 2-back and 0-back conditions.

Behavioral measure	CUD	Control
RT (2-back)	958 ± 142	996 ± 163
In-scanner		
RT (0-back)	749 ± 168	751 ± 159
RT	208 ± 131	245 ± 133
NCR (2-back)	34.7 ± 3.5	34.6 ± 3.5
NCR (0-back)	36.0 ± 4.6	37.4 ± 3.8
NCR	-2.5 ± 8.3	-5.7 ± 5.0
Out-scanner		
Card sorting	117.7 ± 10.6	116.7 ± 9.2
Flanker	110.8 ± 7.3	115.1 ± 10.2
List sorting	110.8 ± 9.7	112.7 ± 11.1

Table 4

The SPM12 second-level random effects one-sample t-test analysis result, across both groups combined, for the contrast of 2-back – 0-back with the cluster level $p < 0.05$ (uncorrected, two-tail). x, y, and z = MNI standard space coordinates (mm). Negative x = Left hemisphere. L = left. R = right.

AAL2 Label	Number of voxels	Maximal t value within the labeled region	MNI coordinates [x y z] (mm) of voxel with maximal t
L precentral gyrus	1123	13.03	-30, 0, 58
R precentral gyrus	495	7.31	44, 6, 30
L superior frontal gyrus	956	11.98	-22, 12, 58
R superior frontal gyrus	1249	12.32	28, 6, 58
L superior orbital frontal cortex	54	5.85	-28, 58, -2
L middle frontal gyrus	2505	12.86	-30, 0, 56
R middle frontal gyrus	3212	12.45	30, 6, 58
L middle orbital frontal cortex	119	4.76	-34, 56, -2
R middle orbital frontal cortex	84	6.55	30, 54, -2
L inferior frontal gyrus pars opercularis	350	9.68	-48, 22, 32
R inferior frontal gyrus pars opercularis	900	8.04	46, 18, 0
L inferior frontal gyrus pars triangularis	943	9.69	-32, 28, 0
R inferior frontal gyrus pars triangularis	625	10.69	42, 36, 26
L inferior frontal gyrus pars orbitalis	116	8.34	-30, 28, -4
R inferior frontal gyrus pars orbitalis	166	9.85	32, 24, -6
L supplementary motor area	792	12.27	-4, 22, 44
R supplementary motor area	653	10.41	4, 22, 46
L medial superior frontal gyrus	622	12.29	-2, 24, 44
R medial superior frontal gyrus	302	11.47	4, 28, 40
L insula	543	10.11	-32, 26, 0
R insula	451	12.12	34, 22, 6
L anterior cingulate cortex	217	5.87	0, 34, 30
R anterior cingulate cortex,	326	7.74	12, 26, 26
L middle cingulate cortex	109	9.23	-2, 30, 36
R middle cingulate cortex	390	11.32	4, 26, 40
L calcarine fissure	280	10.88	-10, -98, -2
R calcarine fissure	122	7.15	14, -92, -6

AAL2 Label	Number of voxels	Maximal <i>t</i> value within the labeled region	MNI coordinates [x y z] (mm) of voxel with maximal <i>t</i>
L lingual gyrus	300	7.37	-14, -92, -2
R lingual gyrus	316	7.65	14, -90, -10
L superior occipital gyrus	154	7.44	-10, -96, 2
R superior occipital gyrus	152	7.09	32, -64, 40
L middle occipital gyrus	496	6.71	-12, -98, 0
R middle occipital gyrus	171	7.54	34, -62, 38
L inferior occipital gyrus	179	7.55	-12, -96, -8
R inferior occipital gyrus	122	5.44	20, -92, -6
L fusiform gyrus	370	5.99	-34, -74, -18
R fusiform gyrus	318	4.37	36, -64, -20
R postcentral gyrus	40	6.03	50, -32, 50
L superior parietal lobule	580	11.02	-32, -60, 44
R superior parietal lobule	368	7.63	14, -60, 52
L inferior parietal lobule	1321	12.48	-38, -54, 46
R inferior parietal lobule	768	12.71	42, -42, 46
R supramarginal gyrus	464	11.83	42, -42, 42
L angular gyrus	261	11.55	-42, -54, 44
R angular gyrus	662	9.12	36, -58, 40
L precuneus	746	11.79	-10, -70, 56
R precuneus	775	8.35	10, -64, 60
L caudate	131	4.46	-14, 0, 16
R caudate	470	5.90	14, 8, 20
L putamen	170	3.92	-18, 8, 8
L thalamus	81	4.33	-2, -18, 14
R thalamus	108	4.79	12, -10, 18

Table 5

The mean (Hz) and posterior probability (PP) of the mean of the modulatory changes (averaged between CUD group and Control group), and the difference in the modulatory changes between the CUD group and the Control group (CUD minus Controls), and between the early-onset CUD individuals and late-onset CUD individuals (early-onset minus late-onset).

CONNECTIVITY	Mean (CUD and control)		CUD minus control		Early minus late	
	MEAN	PP	MEAN	PP	MEAN	PP
L DLPFC → R DLPFC	-0.3334	1.00	0.1194	1.00	0.2435	1.00
L DLPFC → L VLPFC	0	0	0.3457	1.00	0	0
L DLPFC → R VLPFC	0	0	0.2441	1.00	0	0
L DLPFC → L caudate	0	0	0.2405	1.00	0	0
L DLPFC → R caudate	0	0	0.0829	0.6468	0.1909	1.00
R DLPFC → L DLPFC	0	0	-0.1731	1.00	0	0
R DLPFC → L VLPFC	-0.1144	1.00	-0.3595	1.00	0	0
R DLPFC → R VLPFC	0	0	0	0	0	0
R DLPFC → L caudate	-0.2246	1.00	-0.2260	1.00	0	0
R DLPFC → R caudate	-0.2032	1.00	0.2664	1.00	0	0
L VLPFC → L DLPFC	0	0	0.3947	1.00	0	0
L VLPFC → R DLPFC	0.0688	0.5499	0.2156	1.00	-0.3758	1.00
L VLPFC → R VLPFC	0	0	0	0	-0.1101	0.7410
L VLPFC → L caudate	0.3210	1.00	0	0	-0.1505	0.7834
L VLPFC → R caudate	0.3580	1.00	0	0	-0.1415	0.7426
R VLPFC → L DLPFC	-0.4097	1.00	0	0	0	0
R VLPFC → R DLPFC	-0.3996	1.00	0	0	0	0
R VLPFC → L VLPFC	-0.4672	1.00	0.2259	1.00	0	0
R VLPFC → L caudate	-0.2163	1.00	0.1652	1.00	0	0
R VLPFC → R caudate	-0.3523	1.00	0	0	0	0
L caudate → L DLPFC	0.1916	1.00	0	0	0	0
L caudate → R DLPFC	0.2135	1.00	-0.0840	0.6819	0	0
L caudate → L VLPFC	0.2105	1.00	0.1651	1.00	0	0
L caudate → R VLPFC	0.3245	1.00	0.1581	1.00	0	0
L caudate → R caudate	0	0	0	0	0	0

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CONNECTIVITY	Mean (CUD and control)		CUD minus control		Early minus late	
	MEAN	PP	MEAN	PP	MEAN	PP
R caudate→L DLPFC	0.2466	1.00	-0.2680	1.00	0	0
R caudate→R DLPFC	0.2316	1.00	-0.2133	1.00	0	0
R caudate→L VLPFC	0	0	-0.3384	1.00	0	0
R caudate→R VLPFC	0	0	-0.3587	1.00	0	0
R caudate→L caudate	0	0	-0.1669	1.00	0	0

Table 6

The results of the ANOVA analyses. For each of the three analyses, the group factor was CUD and Control, the Pathway factor was the R DLPFC to L caudate and one of the pathways listed in the first column. df = degree of freedom.

Connectivity tested	Main effect of group	Main effect of pathway	Group $\times$ Pathway
R DLPFC→R	$F= 1.65$	$F=0.01$	$F= 76.36$
caudate	df = 1,91	df = 1,91	df = 1,91
	$p= 0.2026$	$p= 0.9284$	$p< 0.0001$
R VLPFC→L	$F= 0.07$	$F= 0.12$	$F= 48.44$
caudate	df = 1,91	df = 1,91	df = 1,91
	$p= 0.7932$	$p= 0.7347$	$p< 0.0001$
L DLPFC→L	$F= 1.35$	$F= 37.64$	$F= 120.30$
caudate	df = 1,91	df = 1,91	df = 1,91
	$p= 0.2481$	$p< 0.0001$	$p< 0.0001$