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CHAPTER 8

NEURAL MECHANISMS OF WORKING-MEMORY & FUTURE CANNABIS USE

This chapter is based on:

Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., Van den Brink, W., Veltman, D.J., Goudriaan, A.E. Working-memory network function in heavy cannabis users predicts changes in cannabis use: a prospective fMRI study, in revision

ABSTRACT

Theoretical models of addiction suggest that a substance use disorder represents an imbalance between hypersensitive motivational processes and deficient regulatory executive functions. Working-memory (a central executive function) may be a powerful predictor of the course of drug use and drug-related problems. Goal of the current functional magnetic resonance imaging (fMRI) study was to assess the predictive power of working-memory network function for future cannabis use and cannabis-related problem severity in heavy cannabis users. Tensor Independent Component Analysis (Tensor-ICA) was used to investigate differences in working-memory network function between 32 heavy cannabis users and 41 non-using controls during an N-back working-memory task. In addition, associations were examined between working-memory network function and cannabis use and problem severity at baseline and at six-month follow-up. Behavioral performance and working-memory network function did not significantly differ between heavy cannabis users and controls. However, among heavy cannabis users, individual differences in working-memory network response predicted weekly cannabis use six months later, over and beyond behavioral predictors of cannabis use: a stronger network response during the N-back task was related to an increase in weekly cannabis use. These findings imply that heavy cannabis users requiring greater effort to accurately complete an N-back working-memory task have a higher probability of escalating cannabis use. Working-memory network function may be a biomarker for the prediction of the course of cannabis use and treatment outcome in cannabis users.

INTRODUCTION

There is great variability in individual vulnerability to develop Substance Use Disorders (SUDs; Swendsen and Le Moal, 2011). Epidemiological studies estimate that only one out of ten weekly cannabis users develops a cannabis use disorder (UNODC World Drug Report, 2009; Perkonigg et al., 2008). To prevent those cannabis users from lapsing into chronic abuse, better understanding of neurobiological processes underlying the progression from recreational substance use towards SUDs is needed.

Despite awareness of reasons why not to use, someone with a SUD continues to use. Theoretical models suggest that SUDs are related to an imbalance between motivational processes and regulatory executive functions (Koob and Volkow, 2010; Robinson and Berridge, 2003; Wiers et al., 2007): Potent and relatively automatically triggered motivations to use (craving; cue-reactivity) combined with deficient executive resources (e.g., disinhibition) promote escalation of substance-use and relapse after abstinence. Therefore, individual differences in executive functioning may be an important contributor to the individual risk to develop SUDs.

Working memory is a central executive function that refers to the capacity to maintain and manipulate online information and its integrity is required for a broad range of cognitive functions (Baddeley, 2010; Kane and Engle, 2002). Working-memory capacity constrains attentional control and is especially important when interfering signals trigger behavioral tendencies conflicting with pursued goals (Kane and Engle, 2002). This suggests that when motivational processes to use are strong, people with good working-memory are better equipped to resist drugs than people with poor working-memory. Indeed, recent studies have shown that individual differences in working-memory capacity moderate the relationship between cognitive motivational processes and (future) substance use (Grenard et al., 2008; Thush et al., 2008). Moreover, interventions that train working-memory have been found effective in improving cognitive dysfunction in stimulant dependent individuals (Bickel et al., 2011), and in reducing alcohol intake in problem drinkers (Houben et al., 2011). Also, both acute and chronic use of various substances of abuse (including cannabis) have been associated with working-memory impairments (Fernandez-Serrano et al., 2011). These findings suggest a bidirectional relationship between working-memory and SUDs and underscore the potential of working-memory improvement as a new tool in the prevention and treatment of SUDs.

The neural network underlying working-memory has extensively been studied with functional Magnetic Resonance Imaging (fMRI). It involves a widespread fronto-parietal network including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), premotor cortex, lateral/medial parietal cortex, paracingulate gyrus, and frontal pole (Owen et al., 2005; Wager and Smith, 2003). Working-memory tasks generally require sustained attention, information storage, memory for temporal order, updating, and manipulation of information. In an attempt to map these functions onto the working-memory network, a meta-analysis of 60 studies

(Wager and Smith, 2003) indicated that the parietal lobe responds to executive demand with a dorsal-ventral dissociation between spatial and non-spatial information. The prefrontal cortex shows a less clear dorsal-ventral dissociation between executive demand and simple information storage, the premotor cortex and DLPFC responding most strongly during updating and remembering temporal order, whereas information manipulation is associated with DLPFC, VLPFC, and frontal pole activation. The paracingulate gyrus is involved when sustained attention is required to perform the task. Since working-memory integrity is required for many cognitive functions, numerous cognitive tasks activate this network and therefore it has been referred to as a more general task-positive network (Fox et al., 2005).

Cannabis use has been shown to affect the functionality of the working-memory network. Cross-sectional studies in cannabis users and controls indicate that moderate to heavy cannabis use is generally associated with normal performance but hyperactivity of the network during a working-memory task (Jacobsen et al., 2007; Jager et al., 2010; Jager et al., 2006; Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2008b; Schweinsburg et al., 2010). These findings support the hypothesis that cannabis users need additional effort to accurately perform the task, reflected in higher working-memory network activations (Jager et al., 2006; Kanayama et al., 2004). However, some studies reported hyperactive areas outside the working-memory network, supporting the alternative hypothesis that cannabis users recruit additional brain areas to accurately perform the task (Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2008b; Schweinsburg et al., 2010). Within cannabis users working-memory network function appears to interact with onset of cannabis use (Becker et al., 2010), nicotine withdrawal (Jacobsen et al., 2007), and alcohol use (Schweinsburg et al., 2011). There are also indications that cannabis abstinence may result in recovery of working-memory (Hanson et al., 2010) and underlying network function (Schweinsburg et al., 2010).

To the best of our knowledge, there are no published studies investigating the relationship between working-memory network function and the course of substance use and the development of substance use related problems. Given its suggested role in the development of SUDs (Grenard et al., 2008; Thush et al., 2008), the goal of the present fMRI study was to assess the predictive power of working-memory network function for future cannabis use and problem severity. A community sample of 32 heavy cannabis users and 41 non-cannabis using matched controls performed an N-back working memory task during which brain activity was recorded. Tensor Independent Component Analysis (Tensor-ICA, Beckmann and Smith, 2005) was used to identify and investigate functional characteristics of the working-memory network (Owen et al., 2005; Wager and Smith, 2003). ICA is a well-established model-free method to detect functional connectivity networks (Beckmann and Smith, 2005). Given that cognitive deficits in neuropsychiatric disorders are generally not restricted to a single brain region (Kim et al., 2009), multivariate approaches may prove to be more sensitive than standard univariate analyses based

on the general linear model (GLM). We expected stronger working-memory network response in heavy cannabis users compared to controls. Moreover, within the group of heavy cannabis users we expected individual differences in network response strength to predict cannabis use and problem severity after six-month follow-up. We further aimed to establish the unique variance explained by this method after controlling for more simple (and cheaper) behavioral indices predicting cannabis use and problem severity.

MATERIALS AND METHODS

The present study was part of a prospective fMRI study investigating the role of neurocognitive processes in predicting the course of drug use in heavy cannabis users (Cousijn et al., 2012a; Cousijn et al., 2011; Cousijn et al., 2012b). In the current report only participants performing the N-back are described. The medical ethical committee of the Academic Medical Centre of the University of Amsterdam approved the study and all participants signed informed consent prior to participation.

Table 1 Sample characteristics

	Heavy cannabis users		**Controls**	
	Baseline	Six-month follow-up	Baseline	Six-month follow-up
N (% female)	32 (34)	30 (34)	41 (37)	41 (37)
Age	21.4 (2.4)	21.9 (2.4)	22.0 (2.3)	22.5 (2.4)
Verbal IQ (Dutch Reading Test)	104.3 (5.4)	--	104.9 (7.4)	--
Alcohol use related problems (AUDIT)	6.2 (3.3)	5.7 (3.3)	5.0 (3.4)	4.7 (3.2)
Cigarette smoking (%)	69	63	17[a]	22[a]
FTND score	2.8 (2.4)	2.9 (2.5)	.5 (1.2)[a]	.6 (1.2)[a]
Cannabis use lifetime (# joints)	1619.5 (1428.9)	1636.7 (1338.1)	4.8 (9.3)	5.3 (10.2)
Cannabis use related problems (CUDIT)	12.5 (5.8)	9.6 (6.6)[b]	0 (0)	.2 (.5)
Duration heavy cannabis use (year)	2.5 (1.9)	3.0 (1.9)	--	--
Current cannabis use days/week	5.0 (1.5)	4.9 (2.1)	--	--
Current cannabis use gram/week	3.1 (2.3)	3.0 (3.0)	--	--
Self-reported abstinence (days)	1.8 (2.3)	--	--	--

Mean (SD). [a] $p < .001$ for group comparison. [b] $p < .05$ baseline follow-up comparison. SD: standard deviation. AUDIT: Alcohol Use Disorder Identification Test. FTND: Fagerström Test for Nicotine Dependence. CUDIT: Cannabis Use Disorder Identification Test.

Participants

Thirty-two heavy cannabis users and forty-one non-cannabis using controls aged 18-25 were recruited through advertisements on the Internet and in cannabis outlets (coffee shops). Groups were matched for age, gender, education, estimated intelligence (Schmand et al., 1991), and alcohol use (Saunders et al., 1993), see Table 1. Heavy cannabis use was defined as using cannabis more than 10 days per month for at least two years and not seeking treatment or having received treatment for cannabis use. Participants in the control group had smoked less than 50 cannabis joints during their lifetime and did not use during the last year (5 controls reported lifetime use of more than 10 joints lifetime). Drug and alcohol use was controlled for by excluding participants with an Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993) score higher than 10, smoking more than 20 cigarettes daily, a positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine, or using non-cannabinoid drugs on more than 100 occasions (5 participants > 10 occasions, no participant > 25 occasions). Other exclusion criteria were general MRI-contraindications, major physical disorders, and psychiatric disorders, which were assessed with the Mini-International Neuropsychiatric Interview [MINI, Dutch version 5.0.0 (Sheehan et al., 1998)]. All participants were asked to refrain from alcohol and drugs (except for nicotine and caffeine) in the 24-hours before testing. Although urine analysis of THC metabolites is insensitive to 24-hour abstinence, it increases accuracy of self-reported substance-use (Roese and Jamieson, 1993). Therefore, urine samples were taken to control for recent illicit substance use (all heavy cannabis users scored positive for cannabis use, whereas all controls scored negative). Testing took place in late afternoon. Participants were financially compensated for their participation.

Questionnaires at baseline and follow-up

Problem severity of cannabis use was assessed with the Cannabis Use Disorder Identification Test (CUDIT; Adamson and Sellman, 2003). The CUDIT is a screening-instrument for at-risk cannabis use and consists of 10 items on cannabis use-frequency and severity of cannabis use-related problems. Severity of nicotine related problems was measured with the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). In addition, a query on past and present cannabis and nicotine use was administered. After six months participants were contacted for a telephone interview on present drug (e.g., cannabis, tobacco, alcohol) use and related problems.

N-back task

Participants performed a letter N-back task during which fMRI-BOLD responses were recorded. The task consisted of alternating blocks with three load levels: 0-back, 1-back, and 2-back. During each block participants were presented with a stream of 15 letters with 5 targets. In 0-back blocks, participants were instructed to indicate when the target letter 'X' appeared on the screen. In 1-back blocks participants had to decide if the letter on the screen was identical to the previous one. In 2-back blocks, targets were those letters identical to the letter presented two trials back. The 0-

back blocks provide a letter recognition baseline, whereas the 1-back and 2-back blocks represent measures of working-memory at low and high load, respectively (Jaeggi et al., 2010). Participants were instructed to press a corresponding button on the right response box for targets and on the left response box for non-targets. The blocks lasted 30s (each stimulus lasted 2 s) and inter-block interval was 5 s, during which the block instructions were repeated. Each load level was repeated four times resulting in a 7 minute task of 12 blocks (Figure 2C). Block order was the same for each participant. Letters were projected on a screen viewed through a mirror attached to the MRI head coil. Prior to scanning the participants briefly practiced the task outside the scanner.

Imaging parameters

A 3T MRI scanner (Philips Intera, Best, The Netherlands) with a phased array SENSE RF eight-channel receiver head coil was used for image acquisition. At start of each scan-session a T1 structural image was acquired (T1 turbo field echo, TR 9.6 s, TE 4.6 ms, 182 slices, slice thickness 1.2 mm, FOV 256 x 256 mm, in-plane resolution 1 x 1 mm, flip angle 8°). During the N-back task, BOLD signal was measured with a T2* gradient-echo EPI sequence (TR 2.29 s, TE 30 ms, 38 slices, slice thickness 3 mm, interslice gap .3 mm, FOV 220 x 220 mm, in-plane resolution 2.3 x 2.3 mm, flip angle 80°). Data pre-processing was conducted with FEAT (FMRI Expert Analysis Tool) version 4.1, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). First, non-brain tissue and skull was removed with BET (Brain Extraction Tool). Images were then slice-time aligned, motion corrected, high-pass filtered in the temporal domain (sigma = 50s), spatially smoothed with a 5mm full-with-half-maximum Gaussian kernel, and prewhitened (Woolrich et al., 2001). Next, functional data were registered to the participants' structural image and transformed to MNI space (Montreal Neurological Institute) using FLIRT (FMRIB's Linear Image Registration Tool).

Statistical analysis

Demographics, scores on questionnaires, and N-back behavioral performance were compared between groups with standard univariate analysis of variance (ANOVA). N-back behavioral performance was assessed in terms of median reaction time of correct responses and accuracy (proportion correct – error responses).

fMRI time-series analysis was carried out using Tensor-ICA (Beckmann and Smith, 2005) implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components), part of FSL. Tensor-ICA enables model-free fMRI analysis of multiple participants and groups by means of a three-way data decomposition into independent components (ICs) representing both signal and artifacts in the data in terms of temporal, spatial, and participant-dependent variations (see Beckmann and Smith, 2005, for a detailed description of Tensor-ICA and a comparison with other methods). Tensor-ICA provides a simultaneous single decomposition of all participant data. It assumes a consistent task-paradigm between participants, which is the case for

the N-back task employed here. The number of ICs is estimated using a Laplace approximation to the Bayesian evidence of the model order. ICs are subsequently calculated by projecting participant data into the eigenvector space of all ICs and optimizing spatial independence between ICs with a measure of non-Gaussianity as ICA cost-function (Beckmann and Smith, 2005). The resulting component maps were thresholded using a Gaussian/Gamma mixture model and an alternative hypothesis approach with a probability threshold of $p > .5$. Finally, each IC was represented by a normalized time-course and a spatial map of normalized z-scores reflecting the degree to which each voxel time-course correlated with the overall IC time-course. Melodic also provides the relative effect-size per participant for a given component, thereby providing information regarding the strength of a component per participant.

After tensor-ICA decomposition, the IC representing the working-memory network as described in a meta-analysis of 24 normative N-back fMRI studies (Owen et al., 2005) was identified. ICs with motion artifacts, a mean power above .1 Hz, or driven by one participant were excluded from analysis. Of the remaining components, spatial maps thresholded at $Z > 2.3$ were compared with the statistical working-memory meta-analysis map thresholded at $Z > 2.3$ (Owen et al., 2005). Overlap between the meta-analysis map and ICs was calculated in terms of percentage significant meta-analysis voxels falling within the thresholded IC map. Talairach Daemon database implemented in FSL and the LONI probability atlas (Shattuck et al., 2008) were used to verify significant cluster locations.

Within the GLM framework implemented in MELODIC it was assessed if the network responded to task load. Differences in network function between heavy cannabis users and controls were investigated in multiple steps. First, individual network effect size (i.e., degree to which individual data contributed to the overall network) was compared between groups to assess differences in individual network response strength. Second, individual structural maps of the network were compared to assess voxel-wise spatial differences. These structural maps were reconstructed from the group network map with a dual regression approach (Filippini et al., 2009), which uses the network time-course in a temporal regression against the individual fMRI data. The individual maps were compared using non-parametric permutation-testing with 10,000 permutations. The resulting group differences maps were thresholded with a TFCE (Threshold-Free Cluster Enhancement) approach (Smith and Nichols, 2009), $p < .05$ corrected for multiple comparisons. Third, activation amplitude of each network area was compared with a simple T-test, Bonferroni corrected for multiple comparisons by dividing the critical p-value of .05 by the total number of tests. For this purpose, percent BOLD signal change for 1-back > 0-back and 2-back > 0-back was quantified per participant for each area within the network with Featquery (implemented in FSL).

Within heavy cannabis users, Pearson correlations were calculated to investigate associations between individual network strength and history of cannabis use, using baseline

weekly use (grams), lifetime use (number of joints), duration of heavy use (years), and baseline problem severity (CUDIT). Hierarchical multiple regression analysis was used to assess the predictive relationship between working-memory network function and weekly cannabis use and problem severity at six months follow-up.

Within the present sample we previously showed that future cannabis use could be predicted by the presence of cannabis approach bias (e.g., faster approach vs. avoid responses) as measured with a joystick Approach-Avoidance Task (Cousijn et al., 2011). During the AAT, participants pushed and pulled a joystick in response to the rotation of cannabis and neutral images. The relative RT difference between cannabis push and cannabis pull responses provides an index of approach bias (Cousijn et al., 2011). Within the hierarchical multiple regression analysis, the predictive relationship between working-memory network function and weekly cannabis use was assessed after controlling for this behavioral cannabis approach bias.

Table 2 Activation amplitude in working-memory network: 1-back vs. 0-back and 2-back vs. 0-back per region in heavy cannabis users and controls

Brain region	MNI coordinates			Z_{max}	*1-bach vs. 0-back*			*2-back vs. 0-back*		
	x	*y*	*z*		cannabis users	controls	*p*	cannabis users	controls	*p*
Frontal pole, L	-38	54	4	5.25	.24 (.05)	.14 (.04)	.12	.44 (.05)	.36 (.05)	.26
Frontal pole, R	34	54	4	4.00	.19 (.05)	.14 (.04)	.41	.36 (.04)	.33 (.05)	.65
VLPFC, L	-30	26	-8	5.27	.23 (.05)	.13 (.03)	.05	.42 (.05)	.38 (.04)	.57
VLPFC, R	34	26	-4	3.86	.26 (.05)	.11 (.04)	.02	.51 (.06)	.37 (.05)	.09
DLPFC, L	-46	10	32	6.81	.21 (.03)	.16 (.03)	.23	.42 (.05)	.46 (.05)	.55
DLPFC, R	50	18	28	4.73	.24 (.04)	.18 (.03)	.24	.42 (.05)	.46 (.04)	.52
Premotor, L	30	10	52	5.33	.25 (.05)	.20 (.03)	.41	.44 (.06)	.48 (.05)	.56
Premotor, R	-26	2	56	5.72	.20 (.03)	.19 (.02)	.88	.39 (.04)	.40 (.03)	.78
PCG, LR	-4	18	44	6.08	.18 (.05)	.16 (.04)	.75	.41 (.06)	.50 (.05)	.26
IPG, L	-34	-54	42	6.40	.25 (.04)	.21 (.03)	.42	.47 (.05)	.53 (.05)	.36
IPG, R	38	-54	44	5.16	.24 (.03)	.19 (.03)	.32	.42 (.04)	.42 (.04)	.96

L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute; MNI coordinates of maximum Z-scores are shown for each region; Values represent average percent signal change over all significant voxels within a region. VLPFC; ventrolateral prefrontal cortex. DLPFC; dorsolateral prefrontal cortex; PCG; paracingulate gyrus. IPG; inferior parietal gyrus

RESULTS

N-back behavioral performance

RTs and accuracy were analyzed using a mixed ANOVA with group (heavy cannabis users vs. controls) as between-subject factor and memory-load as within subject factor with three levels (0-back, 1-back, and 2-back). Analysis of both RTs and accuracy indicated a main effect of memory-load ($F_{2,70}$ = 31.86, p < .001, η^2 = .48 and $F_{2,70}$ = 61.47, p < .001, η^2= . 64 respectively) that did not differ between groups ($F_{2,70}$ = .24, p = .79 and $F_{2,70}$ = 1.58, p = .21 respectively). Consistent with normative N-back performance (Owen et al., 2005), RTs increased (1-back vs. 0-back, t_{72} = 8.18, p < .001, d = .96; 2-back vs. 1-back, t_{72} = 8.85, p < .001, d = 1.04) and accuracy decreased with increasing memory load (1-back vs. 0-back, t_{72} = 2.98, p = .004, d = .35; 2-back vs. 1-back, t_{72} = 5.81, p < .001, d = .68; see Figure 1A and 1B). For the highest memory load, a post hoc t-test indicated that RTs and accuracy during 2-back did not differ between groups (t_{71} = .07, p = .94 and t_{71} = .87, p = .39).

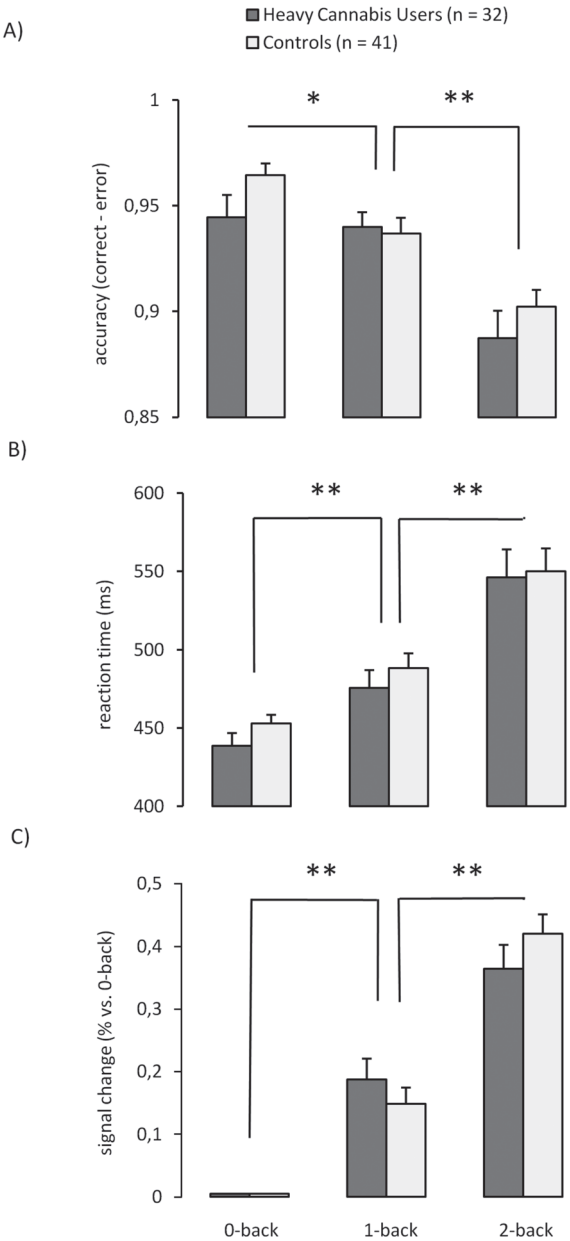
Working-memory network selection

Tensor-ICA reduced the N-back data of 73 participants to 45 ICs explaining 87 % of the variance in the data. Of these components, 18 were excluded from analysis: 9 contained motion artifacts, 2 had a mean power above .1Hz, and 7 were driven by one participant. From the remaining 27 components, the working-memory network was identified. The best matched component showed a 89 % (second-best component 61 %) overlap with the meta-analysis map provided by Owen and colleagues (2005).

Working-memory network functionality

The working-memory network comprised of the bilateral frontal pole, VLPFC, DLPFC, premotor cortex, paracingulate cortex, and inferior parietal cortex (Figure 2A). The network's time-course strongly correlated with the modeled N-back time-course (r = .92, p < .001; Figure 2B. GLM analysis showed that network response strength significantly increased with task load (1-back > 0-back, Z = 18.27, p < .001; 2-back > 1-back & 0-back, Z = 16.87, p < .001; Figure 1C. Network strength did not differ significantly between heavy cannabis users and controls (Z = .31, p = .38). Further, dual-regression analysis indicated that there were no significant voxel-wise spatial differences between groups regarding the working-memory network. Also, activity amplitude of areas within the network did not significantly differ between heavy cannabis users and controls (Table 2). A post-hoc analysis with the 11 other ICs which significantly reacted to task load (p < .001, Bonferroni corrected for number of ICs) also did not reveal significant group differences. Within heavy cannabis users, network strength was not significantly correlated with history of cannabis use and baseline problem severity (r < .13, p > .49).

Figure 1 N-back behavioral performance and network activation per memory load level in heavy cannabis users and controls. **(A)** 0-back, 1-back, and 2-back average group accuracy expressed as proportion correct responses minus errors with standard error bars. **(B)** 0-back, 1-back, and 2-back median group RT of correct responses with standard error bars. **(C)** Working-memory network activity during 1-back and 2-back expressed as percent signal change of 0-back with standard error bars. * $p < .05$, ** $p < .001$.



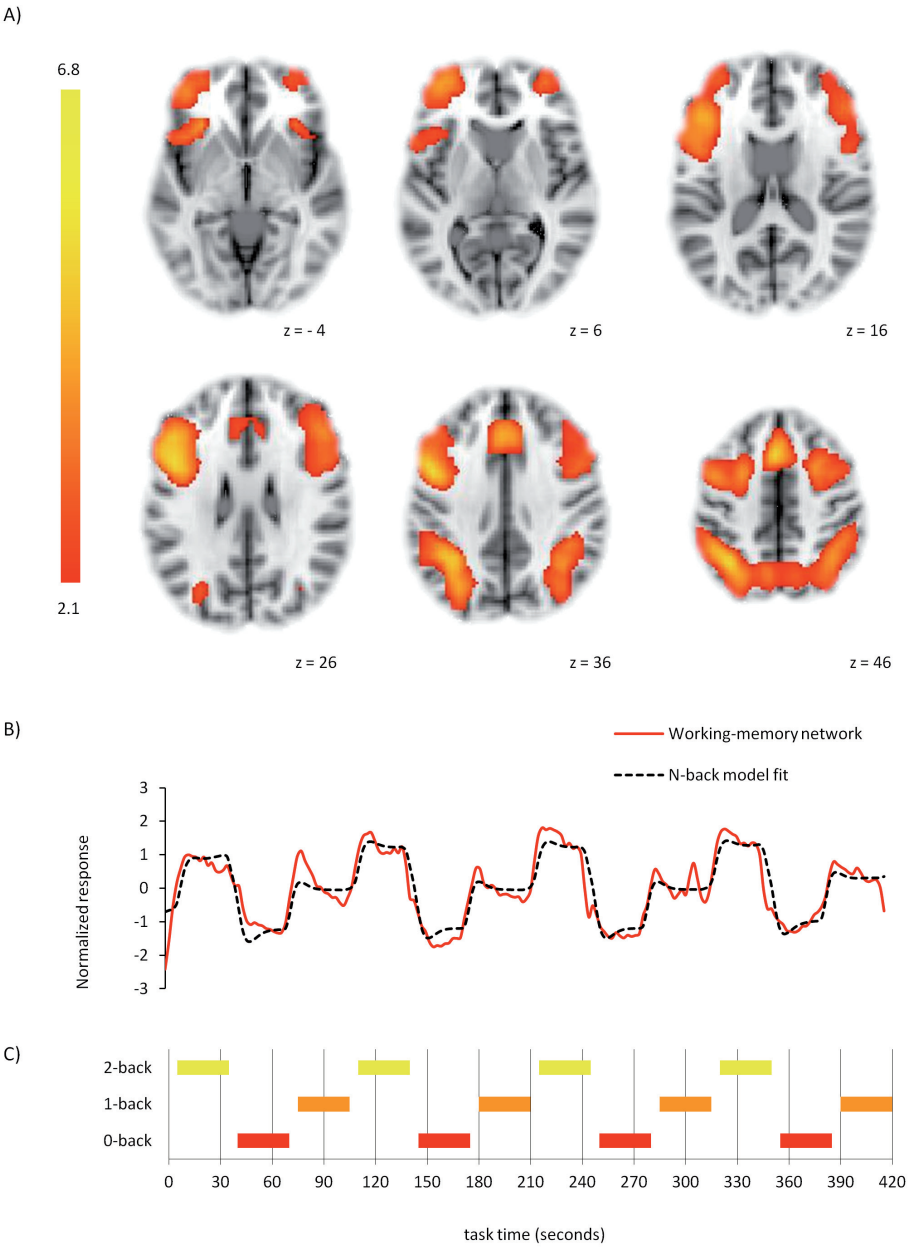
Heavy cannabis users scored higher on measures of nicotine use [smokers (%, $X^2 = 20.05$, $p < .001$); and nicotine related problems (FTND, $t_{71} = 5.44$, $p < .001$)] (Table 1). However, working-memory network strength did not differ between smoking and non-smoking heavy cannabis users and did not correlate with FTND scores.

Predictors of cannabis use after six months

Six months after baseline a 97 % follow-up rate was achieved (two non-responders among the 32 heavy cannabis users). Average cannabis problem severity significantly decreased in heavy cannabis users ($t_{29} = 2.3$, $p = .026$; Table 1). Cannabis use frequencies and measures of alcohol and nicotine use did not change in heavy cannabis users or controls (Table 1).

To assess the predictive relationship between working-memory network function and future cannabis use, a hierarchical multiple regression analysis was performed. Within the present sample, future cannabis use was previously found to be predicted by a cannabis approach bias using the AAT (Cousijn et al., 2011). In the hierarchical regression model, baseline weekly use and approach bias were entered first, after which the working-memory network response strength was entered. Only participants who completed the N-back task, AAT, and follow-up were included in the analysis (n = 29). Preliminary analyses indicated no violation of the assumption of normality, linearity, multicollinearity, and homoscedasticity (maximum Cook's distance = .43, maximum standardized residual = 3.0). The final model explained 70 % of the variance in prospective weekly cannabis use ($F_{3,25} = 19.71$, $p < .001$; Table 3). Baseline weekly cannabis use ($p < .001$) and the approach bias ($p = .0012$) were both significant predictors in the first step and together explained 59 % of the variance in future cannabis use. After correction for variance explained by baseline weekly cannabis use and the approach bias, working-memory network reactivity explained an additional 11 % of the variance in future cannabis use [F change$_{1,25} = 9.20$, $p = .006$ (16 % when approach bias was omitted from the model, F change$_{1,27} = 10.7$, $p = .003$)] Participants with stronger working-memory network reactivity used more cannabis after six months. In the final model, baseline weekly cannabis use and the approach bias remained significant predictors ($p < .001$ and $p = .005$ respectively). No associations were found between working-memory network functionality and future cannabis problem severity.

Figure 2 Spatial and temporal characteristics of the working-memory network extracted by tensor-ICA across groups. **(A)** Spatial characteristics. Significant clusters are overlaid on a standard MNI brain. Right side of the brain is depicted at right side. **(B)** Temporal characteristics. Y-axis: normalized response, x-axis: time (seconds), red line: network time-course, black dotted line: task-model time-course. **(C)** Task-model: order of 0-back, 1-back, and 2-back blocks during N-back task, x-axis: time (seconds).



DISCUSSION

The goal of this fMRI study was to assess the predictive power of working-memory network function for predicting future cannabis use and cannabis-related problem severity in heavy cannabis users. During the N-back working-memory task, both behavioral performance and working-memory network function in terms of strength, location, and activation amplitude did not differ significantly between heavy cannabis users and controls. However, individual differences in working-memory network response strength predicted weekly cannabis use after 6 months in heavy cannabis users, over and beyond behavioral predictors of cannabis use: higher response strength was related to increases in weekly cannabis use. These findings suggest that increased effort during the task (suggestive of a relatively weak working-memory system in cannabis users) is a risk factor for escalating substance use, which is in line with SUD models (Koob and Volkow, 2010; Wiers et al., 2007) and with previous studies on the predictive association between working-memory, motivational processes, and substance abuse (Grenard et al., 2008; Thush et al., 2008). Moreover, these findings indicate that working-memory may be a suitable target for interventions.

The working-memory network identified with tensor-ICA consisted of the bilateral frontal pole, VLPFC, DLPFC, premotor cortex, paracingulate cortex, and inferior parietal cortex, which is consistent with normative working-memory studies (Owen et al., 2005; Wager and Smith, 2003). Over groups, increased memory load was associated with increased network response, slowed behavioral responses, and decreased accuracy. This association between network response and behavioral performance suggests that individual differences in network functionality reflect differences in task difficulty and effort needed to perform the task. Working-memory has been considered a central executive function (Baddeley, 2010; Kane and Engle, 2002) and the underlying network plays a role in many cognitive tasks (Fox et al., 2005). This raises the question whether the association between network function and future cannabis use is unique to working-memory or can be generalized to overall executive functioning. If the latter holds, it predicts that relatively poor network function under any executive function task could be an SUD risk factor. This view is supported by recent behavioral studies (Houben and Wiers, 2009; Wiers et al., 2009a), although more prospective studies are needed to investigate these issues.

Although heavy substance use is prerequisite, SUD risk depends on a complex interaction between numerous factors, varying from person to person (Swendsen and Le Moal, 2011). The balance between sensitized conditioned responses towards substance use and executive control resources is suggested to play an important role in determining SUD vulnerability (Koob and Volkow, 2010; Wiers et al., 2007). Indeed, in the same participants we previously showed that the potent response to automatically approach rather than avoid cannabis (approach bias) predicted unique variance in cannabis use after six months. With a regression analysis that included measures of quantitative substance use, approach bias, and working-memory network function,

we explained a substantial amount (adjusted R^2 67 %) of the variance in future cannabis use, with each measure significantly explaining unique variance. Jointly, these factors may provide us with an integrative model of SUD risk. Interestingly, both working-memory training and approach bias retraining could potentially improve treatment outcome (Bickel et al., 2011; Houben et al., 2011; Wiers et al., 2011; Wiers et al., 2010). However, instead of one standard treatment, the heterogeneity of SUDs calls for personalized treatment (Oslin, 2011). Assessing working-memory network function and strength of approach action tendencies may provide more insight into who will benefit from working-memory training and approach bias-retraining. Future research efforts should be aimed at confirming these inferences.

Table 3 Hierarchical multiple regression analysis for variables predicting weekly cannabis use (gram) at six-month follow-up in heavy cannabis users (n = 29).

	B	SE B	*β*
Step 1: Change R^2 = .59**			
Baseline weekly use	1.28	.22	.75**
Behavioral approach bias	.02	.01	.44*
Step 2: Change R^2 = .11*			
Baseline weekly use	1.14	.20	.67**
Behavioral approach bias	.02	.01	.35*
Working-memory network	.28	.28	.35*

*p < .01 and **p < .001. Final model R^2 = .70**, adjusted R^2 = .67. SE: standard error.

A hyperactive working-memory network has previously been associated with cannabis use (Jacobsen et al., 2007; Jager et al., 2010; Jager et al., 2006; Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2008b; Schweinsburg et al., 2010). Hence, we expected higher working-memory network activations in heavy cannabis users compared to controls. In contrast to our hypothesis, network function and location did not significantly differ between groups (however, a trend was observed in the VLPFC (Table2)]. A post-hoc analysis indicated no group differences in any of the other tensor-ICA networks, arguing against the alternative hypothesis that cannabis users use a compensatory task strategy by recruiting additional brain areas (Kanayama et al., 2004; Padula et al., 2007; Schweinsburg et al., 2008b; Schweinsburg et al., 2010). Equal performance in heavy cannabis users and controls and lack of a significant association between history of cannabis

use and working-memory network reactivity argues against subacute or chronic effects of cannabis on working-memory. The association between cannabis use and working-memory observed in other studies may therefore reflect a pre-existing risk factor rather than a consequence of cannabis use. However, cannabis abstinence may result in recovery of working-memory function (Hanson et al., 2010; Schweinsburg et al., 2010). Moreover, in the current study ceiling effects in the N-Back task [89 % accuracy for the highest memory load (2-back)] may have obscured cannabis induced working-memory deficits.

Some potential limitations must be taken into account. First, there were more smokers among heavy cannabis users and almost all cannabis users (90 %) smoked cannabis combined with tobacco [most common in the Netherlands (Bennett, 2008)]. However, since the heavy cannabis users were relatively light smokers and cigarette smoking was not associated with working-memory network function in heavy cannabis users, it is unlikely that cigarette smoking accounts for the observed effects. However, it may still be worthwhile to include a group of cannabis naive cigarette smokers in future studies in order to better distinguish cannabis from tobacco effects. Also, it should be mentioned that we excluded participants if they had a history of psychiatric disorders; a less stringently selected but more ecologically valid control group may display considerable comorbid externalizing disorders. Therefore, the extent to which the results generalize to all heavy cannabis users remains to be tested.

In summary, the current fMRI study is the first to demonstrate that working-memory network function predicts escalation of cannabis use in heavy cannabis users. This finding implies that heavy cannabis users who require greater effort for adequate N-back working-memory task performance have a higher probability of escalating drug use. As such, working-memory network function may be used to identify individuals at-risk for cannabis use escalation and the development of a cannabis use disorder and may be a new target for prevention and treatment.

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