

Modulation of Mediotemporal and Ventrostriatal Function in Humans by Δ 9-Tetrahydrocannabinol

A Neural Basis for the Effects of Cannabis sativa on Learning and Psychosis

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Context: *Cannabis sativa* use can impair verbal learning, provoke acute psychosis, and increase the risk of schizophrenia. It is unclear where *C sativa* acts in the human brain to modulate verbal learning and to induce psychotic symptoms.

Objectives: To investigate the effects of 2 main psychoactive constituents of *C sativa*, Δ 9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol, on regional brain function during verbal paired associate learning.

Design: Subjects were studied on 3 separate occasions using a block design functional magnetic resonance imaging paradigm while performing a verbal paired associate learning task. Each imaging session was preceded by the ingestion of Δ 9-THC (10 mg), cannabidiol (600 mg), or placebo in a double-blind, randomized, placebo-controlled, repeated-measures, within-subject design.

Setting: University research center.

Participants: Fifteen healthy, native English-speaking, right-handed men of white race/ethnicity who had used *C sativa* 15 times or less and had minimal exposure to other illicit drugs in their lifetime.

Main Outcome Measures: Regional brain activation (blood oxygen level-dependent response), performance in a verbal learning task, and objective and subjective ratings of psychotic symptoms, anxiety, intoxication, and sedation.

Results: Δ 9-Tetrahydrocannabinol increased psychotic symptoms and levels of anxiety, intoxication, and sedation, whereas no significant effect was noted on these parameters following administration of cannabidiol. Performance in the verbal learning task was not significantly modulated by either drug. Administration of Δ 9-THC augmented activation in the parahippocampal gyrus during blocks 2 and 3 such that the normal linear decrement in activation across repeated encoding blocks was no longer evident. Δ 9-Tetrahydrocannabinol also attenuated the normal time-dependent change in ventrostriatal activation during retrieval of word pairs, which was directly correlated with concurrently induced psychotic symptoms. In contrast, administration of cannabidiol had no such effect.

Conclusion: The modulation of mediotemporal and ventrostriatal function by Δ 9-THC may underlie the effects of *C sativa* on verbal learning and psychotic symptoms, respectively.

Arch Gen Psychiatry. 2009;66(4):442-451

CANNABIS SATIVA IS THE world's most widely used illicit drug¹ and has a wide range of cognitive and symptomatic effects.² In healthy individuals, *C sativa* use is associated with acute impairment of learning and memory and induction of psychotic symptoms,^{3,4} while regular users show persistent memory deficits and have increased risk of developing psychotic disorders.^{5,6} The main psychoactive ingredients of *C sativa* are Δ 9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol. Experimental administration of Δ 9-THC can impair learning and induce psychotic symptoms,⁷ although ef-

fects on learning have not been evident in some studies.^{8,9} On the other hand, cannabidiol is anxiolytic,¹⁰ may have antipsychotic properties,¹¹ and does not affect memory performance.^{12,13} Although this suggests that the effects of *C sativa* on learning and psychotic symptoms reflect the action of Δ 9-THC on the brain, this has yet to be demonstrated in humans, and the specific brain regions where it acts to produce these effects have yet to be defined.

Animal investigations indicate that at the molecular level the central effects of Δ 9-THC are mediated by cannabinoid receptors. These receptors have high density in the mediotemporal and prefrontal cor-

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tex,¹⁴ areas critical to learning and memory,^{15,16} and $\Delta 9$ -THC affects mediotemporal and memory function in experimental animals.¹⁷ Therefore, $\Delta 9$ -THC may influence learning and memory by modulating function in these regions. In experimental animals, administration of $\Delta 9$ -THC also increases dopaminergic neuronal firing¹⁸ and striatal dopamine release,¹⁹ which has led to the suggestion that induction of psychotic symptoms by *C sativa* may reflect a secondary effect of $\Delta 9$ -THC on striatal dopamine release.²⁰ Although there is evidence that striatal dopamine activity may mediate acute psychotic symptoms in schizophrenia,²¹ an effect of $\Delta 9$ -THC on striatal dopamine release has not been demonstrated in humans.

Herein, we use functional magnetic resonance imaging following oral challenges with $\Delta 9$ -THC and cannabidiol to directly examine the neural mechanisms underlying the effects of *C sativa* on learning and psychotic symptoms. We tested the hypotheses that $\Delta 9$ -THC would perturb function during a verbal learning task in the mediotemporal and prefrontal cortex and that acute induction of psychotic symptoms would be related to the effects of $\Delta 9$ -THC on activation in the striatum. We also wanted to examine whether the effects of $\Delta 9$ -THC on activation are specific to this compound or are shared by other cannabinoids. We selected cannabidiol because this is the other main psychoactive constituent of *C sativa* and because there is increasing interest in its effects on the brain. Therefore, we tested the hypothesis that $\Delta 9$ -THC, but not cannabidiol, would perturb function during a verbal learning task in the mediotemporal and prefrontal cortex.

METHODS

SUBJECTS

The study protocol was approved by the Joint South London and Maudsley and Institute of Psychiatry National Health Service Research Ethics Committee. Fifteen healthy, native English-speaking, right-handed men of white race/ethnicity who had been exposed to *C sativa* 15 times or less in their lifetime, but not in the previous month, and had minimal exposure to other illicit drugs participated after giving informed consent. Their mean age was 26.7 years, and their mean IQ as measured using the National Adult Reading Test²² was 98.7.

EXPERIMENTAL PROCEDURE

Subjects were imaged using functional magnetic resonance imaging while performing a task that engaged verbal learning. Each subject was imaged on 3 separate occasions, with each session preceded by oral administration of $\Delta 9$ -THC (10 mg), cannabidiol (600 mg), or placebo in a double-blind, randomized, placebo-controlled, repeated-measures, within-subject design.

Two hours before each session, subjects had a light standardized breakfast. One hour before imaging, they were given a gelatin capsule containing $\Delta 9$ -THC (10 mg, approximately 99.6% pure; THC-Pharm, Frankfurt, Germany), cannabidiol (600 mg, approximately 99.9% pure; THC-Pharm), or flour (placebo). Order of drug administration was pseudorandomized across subjects so that an equal number of subjects received any of the drugs during the first, second, or third session. All subjects had a negative urinary drug screen before all sessions. Illicit substance use was assessed using the Structured

Clinical Interview and the Addiction Severity Index,²³ and subjects were advised to abstain from using illicit drugs throughout the duration of the study and to avoid alcohol intake for 24 hours and caffeine intake for 12 hours before the study. Psychopathologic conditions were assessed using the Visual Analog Mood Scale,²⁴ State-Trait Anxiety Inventory by Spielberger,²⁵ Analog Intoxication Scale,²⁶ and Positive and Negative Syndrome Scale (PANSS).²⁷ Heart rate and blood pressure were monitored via a digital recorder and an automated arm cuff. Blood samples were obtained from an indwelling intravenous line in the nondominant arm. Whole-blood drug levels were measured using commercially available agents (Tricho-Tech, Cardiff, England). Psychopathologic ratings and venous blood samples were obtained immediately before and at 1, 2, and 3 hours after drug administration. Imaging was performed between 1 and 2 hours after drug administration. In this study, we focus on the imaging results and report drug levels and behavioral results up to the 2-hour time point.

VERBAL PAIRED ASSOCIATE LEARNING TASK

Subjects performed a verbal paired associate learning task inside the imaging system. The task was adapted from the paired associate learning subtest of the Wechsler Memory Scale-Revised.²⁸ It comprised 3 conditions (encoding, recall, and baseline), with stimuli presented visually in blocks (**Figure 1A**). The accuracy of responses during each condition was recorded online. During encoding, subjects were shown pairs of words and were required to decide whether they went well together (to promote encoding), saying yes or no aloud after each pair. During recall, a word from previously presented pairs was shown next to a question mark, and participants were required to articulate the word that it was previously associated with. Subjects were asked to say "pass" if they could not recall the missing word. The same word pairs were presented in the encoding condition 4 times so that the associations could be learned over repeated blocks. In the baseline condition, subjects were shown pairs of words printed with the same or different fonts. They were required to say whether the same fonts were used for both words in the pair or not, saying yes or no aloud after each pair. The words were different from those presented during the encoding condition, and word pairs were not repeated across blocks to minimize learning to examine brain activation specifically related to learning during encoding and recall. Stimuli were presented in 40-second blocks of 8 stimulus pairs, with 3 conditions presented in the same order (encoding, recall, and baseline) on 4 occasions. Within each encoding block, the order of the word pairs was randomized. A visual prompt preceded each encoding ("Do these words go well together?"), recall ("Which word was associated with this?"), and baseline block ("Are the fonts of these 2 words the same?"). Presenting the same encoding stimulus pairs 4 times across repeated blocks permitted assessment of the effect of learning on activation and recall accuracy. The words presented were taken from the MRC (Medical Research Council) Psycholinguistic Database²⁹ and were similar in terms of number of letters, familiarity,³⁰ written frequency, concreteness, imageability, and meaningfulness. Participants were familiarized with the task during a training session with a set number of trials outside of the imaging system using different words from those presented during imaging.

The blood oxygen level-dependent response of the brain during each encoding and recall block, measured using a 1.5-T magnetic resonance imaging system (GE Medical Systems, Milwaukee, Wisconsin), was contrasted with that during baseline. The effects of $\Delta 9$ -THC and cannabidiol were inferred by contrasting regional brain activation during each condition after each drug administration with that following placebo.

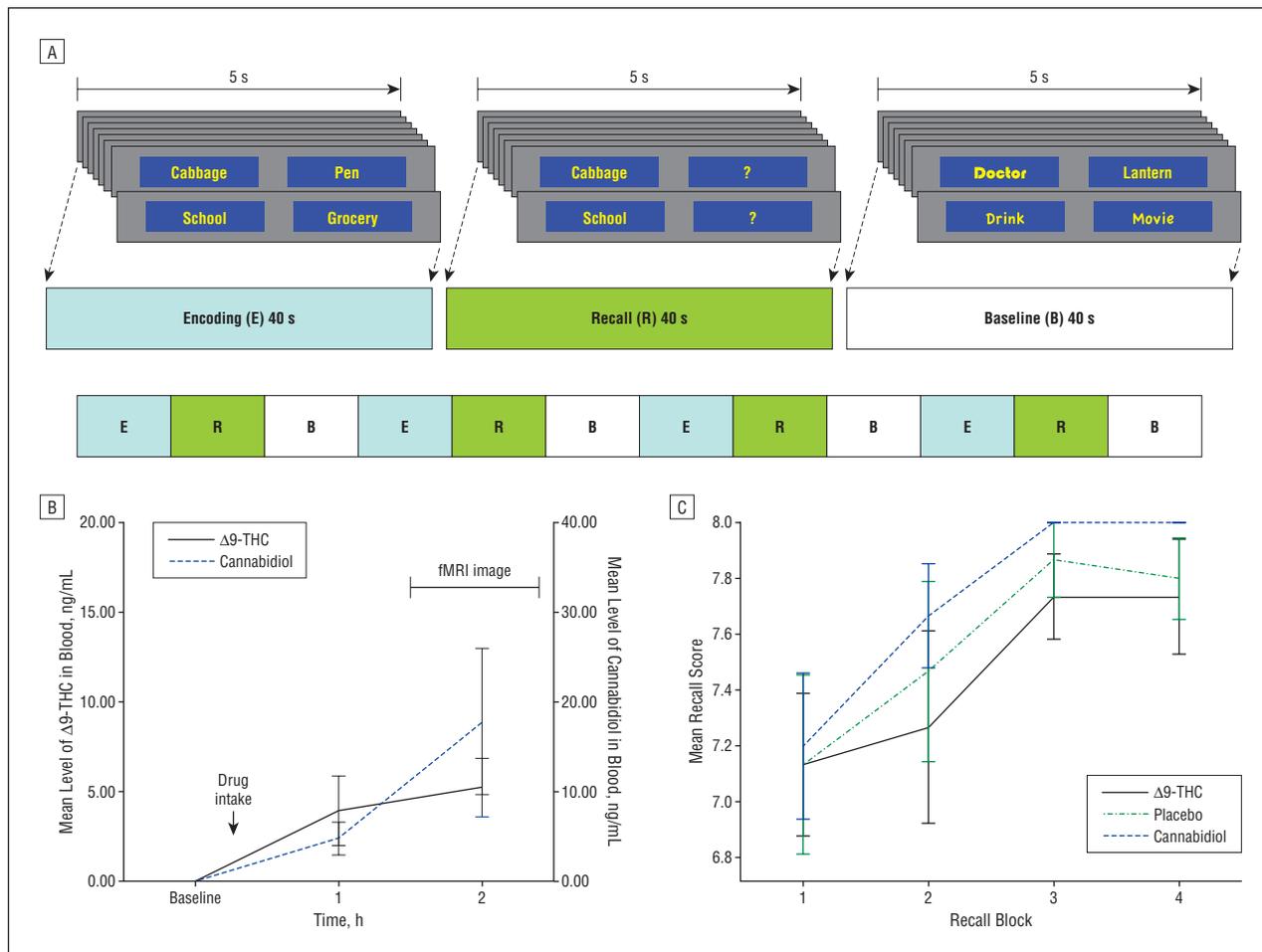


Figure 1. Verbal paired associate learning task, blood levels of drugs, and effect of drugs on task performance. A, Verbal paired associate learning task. B, Plots showing the mean change (error bars show SEM) in levels (y-axis) of $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) (black line) and cannabidiol (dashed blue line) over time (x-axis) following oral intake of $\Delta 9$ -THC and cannabidiol, respectively. Baseline blood samples for drug levels and psychopathologic ratings were obtained immediately before drug intake ($\Delta 9$ -THC, cannabidiol, or placebo capsules) and were repeated after 1, 2, and 3 hours. $\Delta 9$ -Tetrahydrocannabinol and cannabidiol were undetectable in blood in the placebo condition; hence, the plots are not shown. fMRI indicates functional magnetic resonance imaging. C, Plots showing improvement in performance as indexed by the mean recall score (y-axis, error bars show SEM) across the repeated trials (x-axis) of the task shown in A following administration of $\Delta 9$ -THC (black line), cannabidiol (dashed blue line), and placebo (dashed green line). There was no statistically significant effect of session order or drug \times session-order interaction on recall score.

IMAGE ACQUISITION

Images were acquired using the 1.5-T magnetic resonance imaging system. T2-weighted images were acquired with 40-millisecond echo time, 90° flip angle in 16 axial planes (7 mm thick), parallel to the anterior commissure–posterior commissure line. During the verbal paired associate learning task, compressed acquisition with 5-second repetition time and 3.5-second silence was used. A high-resolution inversion recovery image data set was also acquired to facilitate anatomic localization of activation.

DATA ANALYSIS

Functional magnetic resonance imaging data from the verbal paired associate learning task were analyzed using software developed at the Institute of Psychiatry (XBAM version 3.4) using a nonparametric approach to minimize assumptions (<http://www.brainmap.it/>). Images were realigned and smoothed using an 8-mm full-width-at-half-maximum gaussian filter. Individual activation maps were created using 2 γ -variate functions to model the blood oxygen level–dependent response. Following least-squares fitting of this model, a sum of squares (SSQ) statistic was estimated at each voxel. This consisted of the ratio of the SSQ of

deviations from the mean image intensity due to the model (over the whole time series) to the SSQ of deviations due to the residuals. These data were then permuted to determine significantly activated voxels specific to each condition.³¹ The SSQ ratio maps for each individual were transformed into standard stereotactic space,³² and group activation maps were computed for each drug by determining the median SSQ ratio at each voxel. These maps were compared using nonparametric repeated-measures analysis of covariance. The statistical analysis used type I error control to obtain less than 1 false-positive cluster over the whole map. Measures of task performance, symptom ratings, physiologic data, and drug levels were analyzed using repeated-measures analysis of variance (SPSS version 15; SPSS Inc, Chicago, Illinois) to compare drug conditions. When significant differences were found, the Tukey test for pairwise comparisons was applied.

RESULTS

DRUG LEVELS AND BEHAVIORAL MEASURES

The mean (SEM) blood levels of $\Delta 9$ -THC were 3.9 (1.9) and 5.1 (1.6) ng/mL at 1 and 2 hours, respectively (Figure 1B).

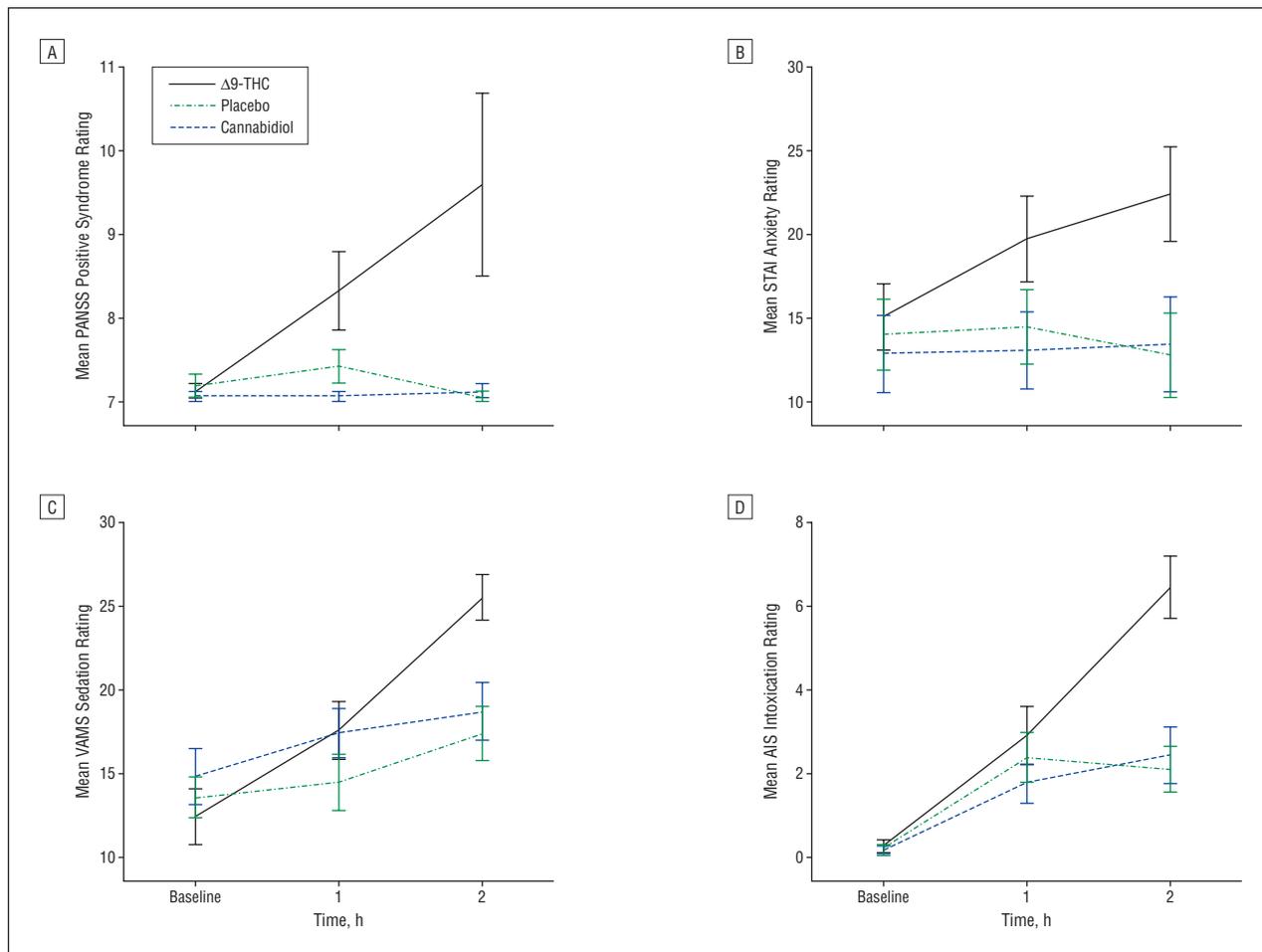


Figure 2. Effect of $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) and cannabidiol on behavior over time. Plots showing changes in psychotic symptoms as indexed by Positive and Negative Syndrome Scale (PANSS) positive symptom ratings (A), anxiety as indexed by State-Trait Anxiety Inventory (STAI) ratings (B), sedation as indexed by Visual Analog Mood Scale (VAMS) mental sedation subscale ratings (C), and intoxication as indexed by Analog Intoxication Scale (AIS) ratings (D) under the effect of $\Delta 9$ -THC (black line), cannabidiol (dashed blue line), and placebo (dashed green line) over time (x-axis). Error bars show SEM. Drug capsules were given soon after baseline measures were obtained, and subsequent ratings were obtained after 1, 2, and 3 hours. Functional magnetic resonance imaging data were acquired between 1 and 2 hours after drug intake. There was no statistically significant effect of session order or drug \times session-order interaction on behavioral symptoms.

The mean (SEM) blood cannabidiol levels were 4.7 (1.8) and 17.7 (8.1) ng/mL at 1 and 2 hours, respectively. No significant effect was noted of either drug on heart rate, blood pressure, or performance in the verbal paired associate learning task as measured by recall score ($P > .05$). However, there was progressive improvement in word recall with repeated presentation of word pairs across encoding blocks for all 3 drug conditions ($F_{1,42} = 22.39, P < .001$), with no significant effect of drug on this repetition-related improvement ($P > .05$). Although $\Delta 9$ -THC administration seemed to be associated with a trend toward slower learning as indexed by slower improvement in recall score across repeated blocks (Figure 1C), this was not statistically significant ($P > .05$). Again, although recall scores were slightly higher following administration of cannabidiol than placebo, this difference was present at baseline, and there was no significant effect of cannabidiol on task performance across repeated blocks ($P > .05$). We also identified a nonsignificant trend for an increase in heart rate with $\Delta 9$ -THC (mean [SEM], 1.93 [5.74] and 8.79 [16.31] beats/min at 1 and 2 hours after baseline). Administration of $\Delta 9$ -THC was associated with acute induction of psychotic symptoms (PANSS positive syndrome

subscale; $F_{1,88} = 7.53, P = .007$), anxiety (State-Trait Anxiety Inventory state subscale; $F_{1,88} = 7.45, P = .008$), sedation (Visual Analog Mood Scale mental sedation subscale; $F_{1,88} = 6.96, P = .01$), and intoxication (Analog Intoxication Scale; $F_{1,88} = 14.37, P < .001$) compared with placebo (Figure 2). PANSS total score ($F_{1,88} = 14.12, P < .001$), negative syndrome subscale score ($F_{1,88} = 9.29, P = .003$), and general psychopathology subscale score ($F_{1,88} = 11.81, P = .001$) were also significantly increased by $\Delta 9$ -THC administration (eFigure 1; <http://www.archgenpsychiatry.com>). In contrast, following administration of cannabidiol, no significant change was noted in psychotic symptoms (PANSS positive syndrome subscale), anxiety (State-Trait Anxiety Inventory state subscale), sedation (Visual Analog Mood Scale mental sedation subscale), or intoxication (Analog Intoxication Scale), nor in PANSS total score, negative syndrome subscale score, or general psychopathology subscale score compared with placebo (Figure 2 and eFigure 1) ($P > .05$). There was also no significant effect of order of drug administration and no interaction between the effects of drug and order of administration on any of the psychopathologic measures or on recall score.

Table. Talairach Coordinates for Peak Areas of Activation Modulated by Verbal Paired Associate Learning Task and by Task × Drug Interaction

Area	Talairach Coordinate			Cluster Size	P Value ^a
	x	y	z		
Linear decrease in activation over repeated encoding blocks in placebo condition					
Parahippocampal gyrus	7	-37	-2	64	.001
Precuneus	4	-59	48	41	.004
Lingual gyrus	18	-63	-7	30	.004
Cerebellum	-7	-52	-35	21	.004
Retrosplenial cingulate	-4	-44	9	16	.001
Comparison of linear change in activation over repeated encoding blocks, placebo vs Δ 9-tetrahydrocannabinol					
Midbrain	-7	-26	-18	25	.005
Cerebellum	7	-63	-18	23	.005
Parahippocampal gyrus	7	-37	-2	14	.002
Comparison of linear change in activation over repeated encoding blocks, placebo vs cannabidiol ^b					
Insula	-36	-22	15	19	.01
Midtemporal gyrus	36	-48	9	19	.02
Lingual gyrus	14	-59	4	16	.02
Precuneus	18	-74	37	14	.02
Precentral gyrus	43	-19	42	12	.01
Linear decrease in activation over repeated recall blocks in placebo condition					
Dorsoanterior cingulate and medioprefrontal cortex	7	44	4	25	.01
Comparison of linear change in activation over repeated recall blocks, placebo vs Δ 9-tetrahydrocannabinol					
Ventral striatum	-7	11	-7	16	.001
Rostroanterior cingulate	-18	22	-13	8	.001
Dorsoanterior cingulate and medioprefrontal cortex	-18	37	26	6	.001
Comparison of linear change in activation over repeated recall blocks, placebo vs cannabidiol ^b					
Hippocampus	28	-22	-13	25	.01

^aCorrected for less than 1 false-positive cluster.

^bClusters do not survive the statistical threshold for less than 1 false-positive cluster.

EFFECT OF TASK AND DRUGS ON BRAIN ACTIVATION

Under placebo conditions, presentation of word pairs across repeated encoding blocks was associated with progressive improvement in recall score (Figure 1C) and linear reduction in engagement of various areas, including the parahippocampal and retrosplenial cingulate cortex and the precuneus bilaterally (Table). Furthermore, the decrement in parahippocampal response was directly correlated with recall score ($r=0.502$, $P=.03$) (Figure 3A). Administration of Δ 9-THC augmented parahippocampal activation during blocks 2 and 3 such that the normal linear decrement in activation across repeated encoding blocks (Figure 3) and its relationship with the recall score were no longer evident.

Repetition of the recall condition under placebo conditions was associated with linear reduction in activation of the dorsoanterior cingulate and medioprefrontal cortex bilaterally (Table), and this decline in activation was correlated with recall score ($r=0.619$, $P=.007$). Administration of Δ 9-THC augmented activation in the left dorsoanterior cingulate and medioprefrontal cortex such that there was no longer a linear reduction in response or a correlation between the change in activation and recall score.

Δ 9-Tetrahydrocannabinol administration also attenuated activation during recall in the striatum bilaterally and

the left rostroanterior cingulate gyrus (Figure 4A and Table). Under placebo conditions, response in these regions gradually increased nonsignificantly across repeated recall blocks (Figure 4B). Administration of Δ 9-THC attenuated this response, and in the ventral striatum and the rostroanterior cingulate cortex, this effect was directly correlated with severity of psychotic symptoms concurrently induced by Δ 9-THC ($r=0.568$, $P=.01$ and $r=0.506$, $P=.03$, respectively) (Figure 4C). This relationship between psychotic symptoms and the effect of Δ 9-THC in the ventral striatum persisted after excluding an outlier identified using Cook's D reliability analysis ($r=0.465$, $P=.047$). However, the relationship between psychotic symptoms and activation in the rostroanterior cingulate cortex did not remain significant after excluding the outlier ($r=0.388$, $P=.09$). Therefore, in the ventrostriatal cluster, attenuation of activation was greatest in the subjects who became most psychotic. This relationship between symptoms and brain activation was not evident in any other brain region and was specific to psychotic symptoms (it was not evident in relation to anxiety, intoxication, or sedation).

In contrast to Δ 9-THC, cannabidiol administration modulated activation in a different set of areas in the brain during repeated encoding and recall blocks relative to placebo (Table and eFigure 2). However, these areas did not reach the statistical threshold corrected for less than 1 false-positive cluster.

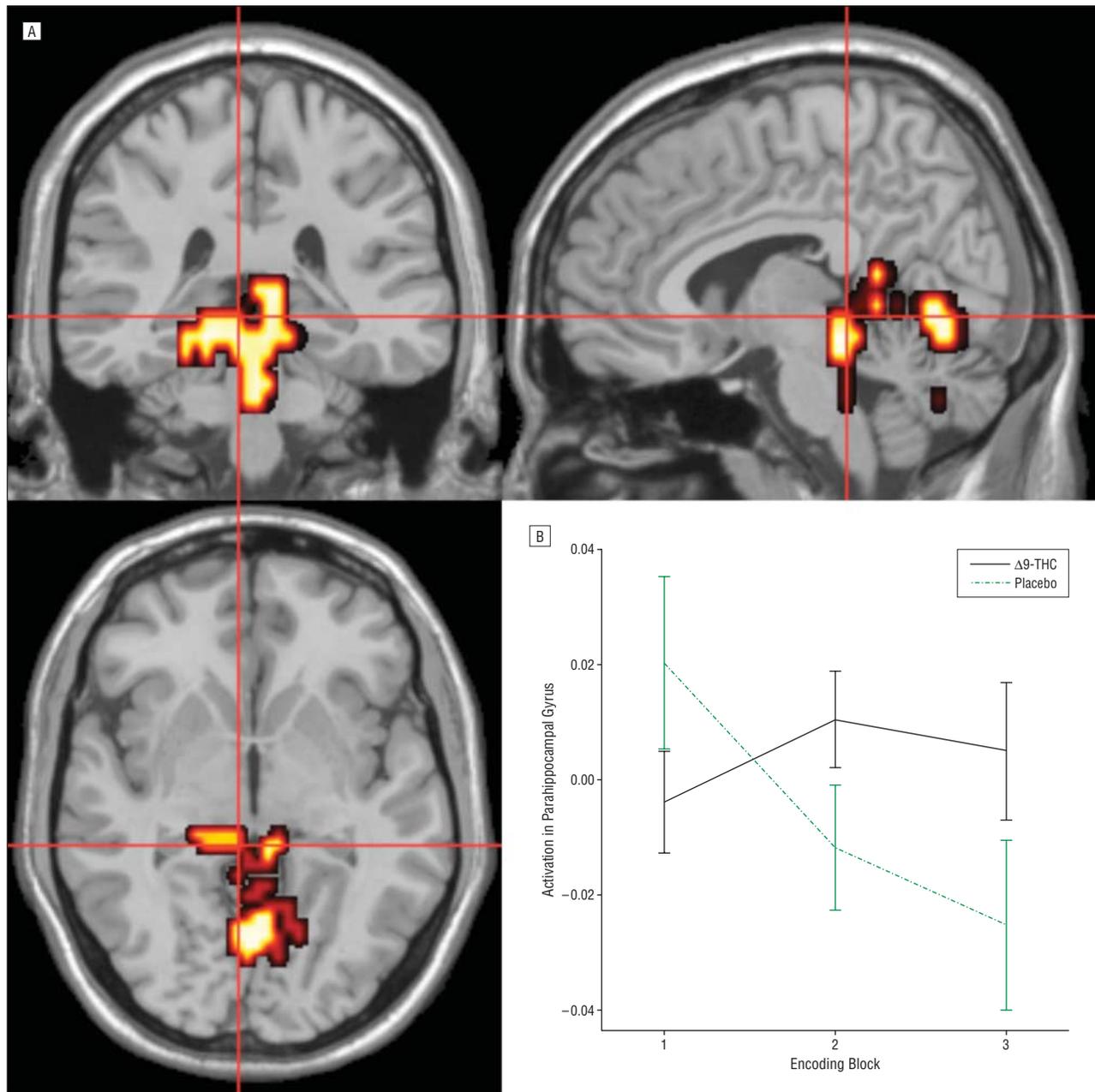


Figure 3. Effect of $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) on brain activation during verbal learning. A, Administration of $\Delta 9$ -THC diminished change in activation across repeated presentations of word pairs during the encoding condition that was evident in the parahippocampal gyri (crosshair) bilaterally under placebo conditions ($P=.002$, corrected for <1 false-positive cluster; peak focus $x=7$, $y=-37$, and $z=-2$ coordinates in Talairach space). $\Delta 9$ -Tetrahydrocannabinol also modulated activation in the midbrain and cerebellum. Change in activation over repeated encoding blocks under the placebo condition showed a decremental pattern in the cerebellum but not in the midbrain. The left side of the brain is shown on the left side of the images. B, Plots showing the mean magnitude of activation (indexed by the mean sum of squares ratio, y-axis; error bars show SEM) in the parahippocampal gyral cluster shown in A) during each encoding block (x-axis) following administration of $\Delta 9$ -THC (black line) and placebo (dashed green line). The plots of activation show the pattern of change in the effect of $\Delta 9$ -THC over time in the parahippocampal region using the mean of the values from all voxels in the cluster. This measure was not used in the statistical analysis, which instead examined the effect at each voxel independently.

COMMENT

The mediotemporal cortex has a central role in verbal information encoding and, more specifically, in relational memory binding.^{15,33} The linear decrement in engagement of this region that we observed during learning under placebo conditions is consistent with previous findings.³⁴ In the present study, the mediotemporal localization of this time-dependent response and its relationship with recall

score are consistent with its role in encoding. Augmentation of this response by $\Delta 9$ -THC and elimination of the relationship between mediotemporal activation and recall score are consistent with evidence that $\Delta 9$ -THC impairs mediotemporal function in animals¹⁷ and memory performance in animals and humans^{7,8,17} and may reflect increased demands on encoding under the influence of $\Delta 9$ -THC. To our knowledge, the acute effect of *C sativa* on episodic memory has not been studied using neuro-

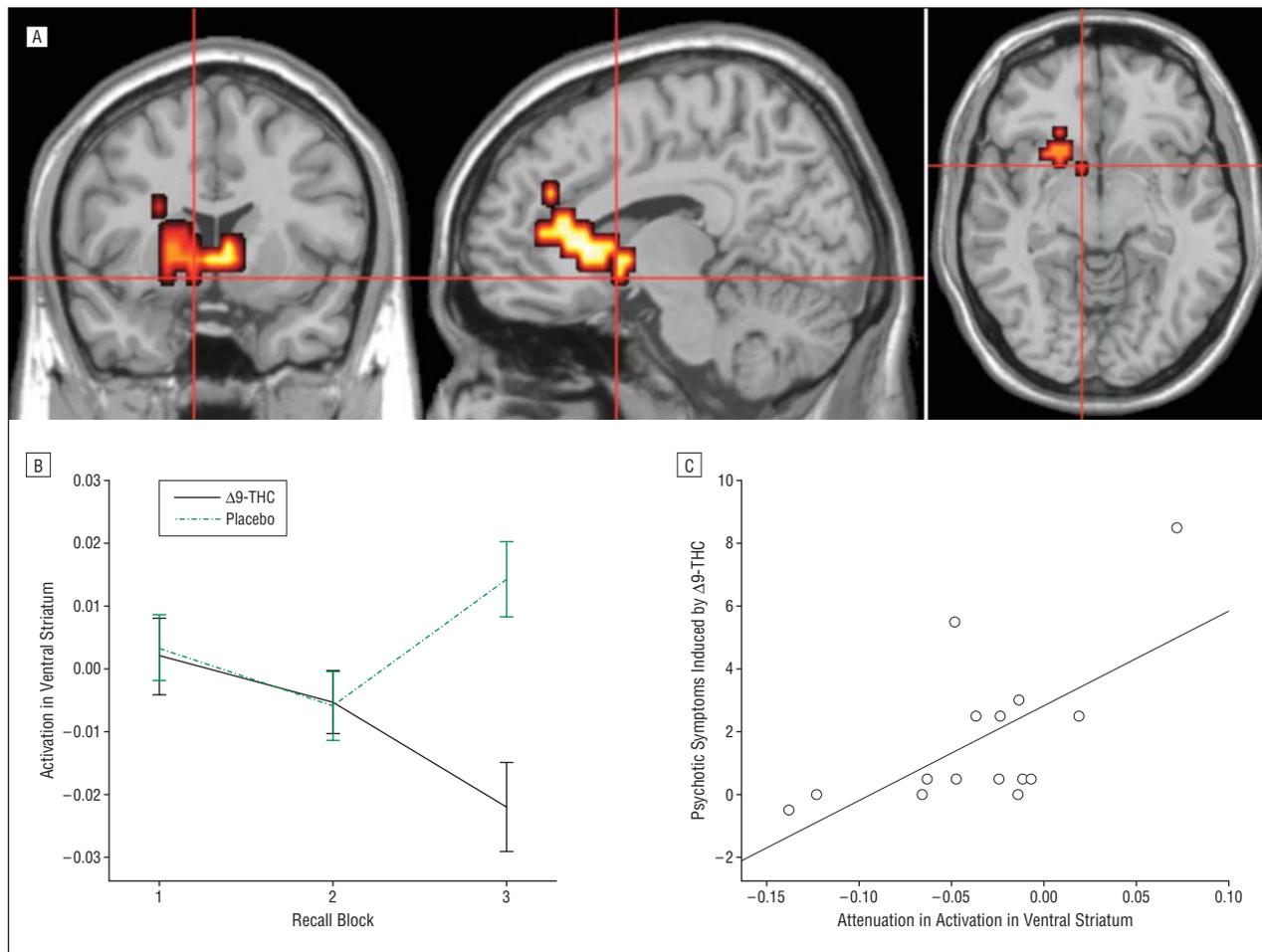


Figure 4. Effect of $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC) on brain activation during repeated recall trials and relationship with symptoms. **A**, Administration of $\Delta 9$ -THC attenuated activation in the ventral striatum ($P = .001$, corrected for < 1 false-positive cluster; crosshair at peak focus $x = -7$, $y = 11$, and $z = -7$ coordinates in Talairach space) and the rostromedial cingulate cortex ($x = -18$, $y = 22$, and $z = -13$) across repeated recall blocks, abolishing the increment in activation under the placebo condition. The left side of the brain is shown on the left side of the images. **B**, Plots showing the mean magnitude of activation (indexed by the mean sum of squares [SSQ] ratio, y-axis; error bars show SEM) in the ventrostriatal cluster shown in **C** during each recall block (x-axis) following administration of $\Delta 9$ -THC (black line) and placebo (dashed green line). The plots of activation show the pattern of change in the effect of $\Delta 9$ -THC over time in the ventrostriatal cluster using the mean of the values from all voxels in the cluster. This measure was not used in the statistical analysis, which instead examined the effect at each voxel independently. **C**, Plot showing correlation between attenuation of activation in the ventral striatum (indexed by change in median SSQ ratio, x-axis) caused by $\Delta 9$ -THC across repeated recall blocks and psychotic symptoms (y-axis) induced by it.

imaging before, although an electrophysiologic study³⁵ demonstrated that administration of *C sativa* impaired task performance and attenuated the amplitude of event-related potentials. Our findings are consistent with this. Effects of $\Delta 9$ -THC on mediotemporal activation might also contribute to persistent deficits in verbal learning and memory seen in regular *C sativa* users.⁵

$\Delta 9$ -Tetrahydrocannabinol also augmented activation in the left dorsoanterior cingulate and the medio-prefrontal cortex during recall, abolishing the linear decline in response across repeated blocks seen under placebo conditions and the correlation between this response and the progressive improvement in recall score. Anterior cingulate and medioprefrontal activation in this context has been related to retrieval monitoring and verification,³⁶⁻³⁸ suggesting that this effect of $\Delta 9$ -THC may be a correlate of increased demands on these processes in the presence of the drug.

The correlation between the effects of $\Delta 9$ -THC on activation in the ventral striatum and the rostromedial cin-

gulate cortex and the provocation of psychotic symptoms is consistent with evidence that the striatum and the cingulate are rich in cannabinoid receptors.¹⁴ The striatum and the cingulate have been implicated in the pathogenesis of psychotic symptoms in schizophrenia.³⁹

None of these effects were evident following administration of cannabidiol. This is consistent with evidence that cannabidiol does not affect learning and memory^{12,13} and indicates that the effects of *C sativa* on memory and psychotic symptoms may be specifically related to its $\Delta 9$ -THC content.

It is possible that the potential effect of articulation during the task on brain activation influenced our results. We sought to minimize the risk of this by collecting functional magnetic resonance imaging data using a sequence in which image acquisition was compressed into the initial part of each repetition time, creating a "silent" period when images were not being acquired and the imaging system did not produce acoustic noise.⁴⁰ Verbal responses during the task were restricted to these si-

lent periods. This meant that any head movement associated with articulation occurred outside of the time when the images were being acquired, reducing the likelihood of stimulus motion–correlated artifacts.⁴¹ In addition, because there was no acoustic imaging system noise, subjects did not need to shout their responses. Findings in the present study were obtained from comparisons of repetitions on the same condition and from comparisons of the effects of drugs on the same conditions. The verbal responses in these comparisons were identical. Therefore, even if articulation had affected the functional magnetic resonance imaging signal, it would have to have had a systematically different effect in identical blocks on the same condition or on the same condition in the presence of one drug vs another. This seems unlikely because there was no change in the demands on articulation across repetitions of the task or between drug conditions, and there was no significant difference in the performance of the task between drug conditions. Therefore, we think it is unlikely that subjects' verbal responses significantly affected the results.

It is also possible that processes other than learning (such as changes in attention or habituation due to repeated presentation of the same stimuli) could have contributed to the progressive reduction in parahippocampal activation. The present study was not intended to disentangle the relative contributions of learning from those of habituation or changes in attention. Nevertheless, had the latter processes been responsible for the findings, one might have expected similar results across repeated recall blocks as in the encoding blocks because both involved presentation of the same verbal stimuli (1 word of a pair or word pairs). However, the linear change in parahippocampal activation across presentations was specific to the encoding condition. Similarly, if this change in parahippocampal activation had been related to increased ease of responding across repeated presentations, this would have applied to both the recall and encoding conditions. Nevertheless, we further examined (data not shown) the pattern of activation associated with repeated presentation of stimuli independent of demand on verbal learning (ie, across both encoding and recall conditions), which was associated with linear decline in engagement of areas other than the mediotemporal lobe, specifically the precuneus, cerebellum, and occipital cortex. This suggests that habituation and changes in attention across repeated presentations were associated with changes in activation in these areas, but this could not account for the change in parahippocampal activation. Finally, we found that parahippocampal activation was modulated by $\Delta 9$ -THC during the encoding condition but not during the recall condition. If this drug effect had been related to an influence on attention, habituation, or ease of responding, one might have expected a similar drug effect across repetitions of the recall stimuli (which there was not). Similarly, repeated presentation of stimuli independent of demand on verbal learning (ie, across both encoding and recall conditions) was associated with a linear increase in engagement of the centrosulcal cortex (data not shown) but not the anterocingulate cortex and the medioprefrontal region, where $\Delta 9$ -THC had an effect during repetition

of the recall condition. This suggests that nonspecific changes due to repeated presentation of stimuli during the recall condition could not account for the decline in activation in the anterocingulate cortex and the medioprefrontal region under the placebo condition nor for the modulation of this effect by $\Delta 9$ -THC.

One may also conclude that the results of the present study do not reflect the neural underpinnings of $\Delta 9$ -THC–induced impairment in verbal learning, as there was no modulatory effect of drug on performance during the learning task. However, the objective of the present study was not to examine the effects of $\Delta 9$ -THC on behavioral performance during a verbal learning task, which has been examined in previous investigations.⁹ Our objective was to assess the effects of $\Delta 9$ -THC and cannabidiol on the neural bases of verbal learning. The task was made easy to ensure that performance across the drug conditions would be matched so that any differences in brain activation between the drug conditions could be interpreted without the confounding effect of differential task performance. Therefore, the study was powered to detect effects at the neurophysiologic level as opposed to the behavioral level, and absence of effects on task performance is not surprising. Absence of significant effects at the behavioral level does not preclude significant effects at the neurophysiologic level.⁴² Indeed, this is often considered desirable in functional imaging investigations, as it reduces the risk that effects on brain function are a nonspecific consequence of impaired task performance.⁴³ In the present study, absence of effects on task performance allowed us to interpret any differences in brain activation between the drug conditions without the confounding effect of differential task performance. Therefore, the modulatory effects of $\Delta 9$ -THC on mediotemporal, anterocingulate and medioprefrontal, and striatal activation during verbal learning were observed even though the conditions were matched for recall performance.

Previous neuroimaging evidence has demonstrated that acute administration of $\Delta 9$ -THC modulates brain activity,⁴⁴ but these effects were difficult to relate to specific cognitive processes because subjects were imaged in the resting state. Neuroimaging investigations that have used cognitive tasks have mainly compared activation in regular *C sativa* users with that in control subjects, and although group differences have been reported, the results have been inconsistent.^{45–47} This may reflect confounding effects of differences between substance users and control volunteers, as well as variation in duration of *C sativa* use, its dose, and its pharmacologic composition. To date, the present investigation is the first to have studied acute effects of both $\Delta 9$ -THC and cannabidiol during a verbal learning task. Using a within-subject design in volunteers with minimal previous *C sativa* exposure minimized the confounding effects of differences between substance users vs controls and chronic *C sativa* use.

To our knowledge, this is the first demonstration in humans that $\Delta 9$ -THC modulates mediotemporal and anterocingulate and medioprefrontal cortex function in the context of learning and induces psychotic symptoms by modulating ventrostriatal activity. Evidence

that $\Delta 9$ -THC influences function in these regions provides a plausible mechanism for increased risk of schizophrenia in regular *C sativa* users,⁶ as the medio-temporal, anterocingulate and medioprefrontal cortex, and striatum are critically implicated in the pathogenesis of the disorder.⁴⁸

Submitted for Publication: May 2, 2008; final revision received August 7, 2008; accepted September 3, 2008.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by a grant from the Psychiatry Research Trust. Dr Bhattacharyya is supported by a joint Medical Research Council and Priory clinical research training fellowship from the Medical Research Council. Dr Crippa is recipient of a Conselho Nacional de Desenvolvimento Científico e Tecnológico Productivity fellowship.

Additional Contributions: Dr Nosarti adapted the task from the Paired Associate Learning subtest of the Wechsler Memory Scale—Revised. Glynis Ivin, BPharm, helped with the blinding procedure, storage, and dispensing of the drugs, and Mick Brammer, PhD, provided helpful suggestions.

Additional Information: The eFigures are available at <http://www.archgenpsychiatry.com>.

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