ORIGINAL ARTICLE

Induction of Psychosis by Δ9-Tetrahydrocannabinol Reflects Modulation of Prefrontal and Striatal Function During Attentional Salience Processing

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Context: The aberrant processing of salience is thought to be a fundamental factor underlying psychosis. Cannabis can induce acute psychotic symptoms, and its chronic use may increase the risk of schizophrenia. We investigated whether its psychotic effects are mediated through an influence on attentional salience processing.

Objective: To examine the effects of Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) on regional brain function during salience processing.

Design: Volunteers were studied using event-related functional magnetic resonance imaging on 3 occasions after administration of Δ9-THC, CBD, or placebo while performing a visual oddball detection paradigm that involved allocation of attention to infrequent (oddball) stimuli within a string of frequent (standard) stimuli.

Setting: University center.

Participants: Fifteen healthy men with minimal previous cannabis use.

Main Outcome Measures: Symptom ratings, task performance, and regional brain activation.

Results: During the processing of oddball stimuli, relative to placebo, Δ9-THC attenuated activation in the right caudate but augmented it in the right prefrontal cortex. Δ9-Tetrahydrocannabinol also reduced the response latency to standard relative to oddball stimuli. The effect of Δ9-THC in the right caudate was negatively correlated with the severity of the psychotic symptoms it induced and its effect on response latency. The effects of CBD on task-related activation were in the opposite direction of those of Δ9-THC; relative to placebo, CBD augmented left caudate and hippocampal activation but attenuated right prefrontal activation.

Conclusions: Δ9-Tetrahydrocannabinol and CBD differentially modulate prefrontal, striatal, and hippocampal function during attentional salience processing. These effects may contribute to the effects of cannabis on psychotic symptoms and on the risk of psychotic disorders.

Arch Gen Psychiatry. 2012;69(1):27-36

Cannabis, and its main psychoactive ingredient Δ9-tetrahydrocannabinol (Δ9-THC), can induce acute psychotic symptoms in healthy individuals,[1,2] exacerbate preexisting psychotic symptoms in patients with schizophrenia,[3] and increase the risk of schizophrenia after long-term use.[4] Psychotic symptoms in schizophrenia are related to increased dopaminergic activity in the striatum,[5] which is thought to lead to the attribution of salience[6] to what would normally be insignificant experiences or stimuli. Aberrant salience attribution has been related to the presence of delusions[7] and to abnormal striatal activation in patients with schizophrenia.[8,9]

Acute administration of Δ9-THC modulates dopamine levels[10] and task-related activation in the striatum.[2] Under the influence of cannabis, users report that banal sensory stimuli or commonplace conversation acquire new meanings and significance[11] and that they experience perceptual alterations; these phenomena have been interpreted as reflecting altered salience processing.[12-14] Central cannabinoid (CB1) receptors, the principal target of Δ9-THC in the brain, modulate the acquisition and expression of learned, emotionally salient conditioned associations in rats.[15] However, whether Δ9-THC modulates salience processing in humans and the extent to which this underlies the psychotogenic effects of Δ9-THC have yet to be investigated.

In addition to Δ9-THC, *Cannabis sativa* contains cannabidiol (CBD), which has quite different effects. Coadministration of CBD with Δ9-THC can block the effects of

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Δ9-THC on psychotic symptoms,[16-18] consistent with evidence that CBD and Δ9-THC may have opposing effects on CB1 receptors[19] and on regional brain activation.[20] Moreover, Δ9-THC can induce acute psychotic and anxiety symptoms, and CBD may have anxiolytic[21,22] and antipsychotic effects.[23-25] Recent evidence[26] suggests that CBD can attenuate the incentive salience of drug and food cues under the influence of Δ9-THC by reducing the attentional bias to these stimuli in humans, complementing evidence from animal studies[27,28] that, although Δ9-THC enhances the salience of drugs of abuse, CBD may have the opposite effect.[29]

The aim of the present study was to examine the acute effects of Δ9-THC and CBD on brain function during the processing of salient and nonsalient stimuli. We used event-related functional magnetic resonance imaging (fMRI) to study healthy volunteers with minimal previous cannabis exposure in a placebo-controlled repeated-measures design. Participants were evaluated while performing a visual oddball task that assessed the allocation of visuospatial attention to salience. Previous studies in identical or similar paradigms implicate the prefrontal cortex,[30-32] medial temporal cortex,[33-37] and striatum[37,38] in processing salience related to the novelty, deviance, or rareness of stimuli.[31,32] We tested the hypothesis that administration of Δ9-THC would perturb salience processing, leading to faster responses to standard stimuli relative to oddball stimuli and altering activation in the prefrontal cortex, hippocampus, and striatum. On the basis of previous findings,[2] we predicted that the induction of positive psychotic symptoms by Δ9-THC would be associated with its effects on activation in the striatum. Our final hypothesis was that the effects of CBD on activation in the prefrontal cortex, medial temporal cortex, and striatum would be in the opposite direction to those of Δ9-THC, as described in the context of other paradigms.[20]

METHODS

We examined 15 healthy men (mean [SD] age, 26.67 [5.7] years; IQ, 98.67 [7.0], as measured using the National Adult Reading Test[39]) during 3 sessions in a double-blind, placebo-controlled, within-subject design with counterbalanced order of drug administration using an established protocol,[2] described in detail in the eMethods (http://www.archgenpsychiatry.com). Participants were scanned 3 times, with at least a 1-month interscan interval in a university center. All participants provided written informed consent. The study was approved by the local research ethics committee, and the investigators had a license to use Δ9-THC and CBD for research.

All participants were occasional cannabis users and had negative findings on a urine drug screen for amphetamines, benzodiazepines, cocaine, opiates, and Δ9-THC before each session. One hour before scanning, participants were given identical gelatin capsules of Δ9-THC, 10 mg; CBD, 600 mg (THC Pharm); or placebo (flour). Psychopathologic ratings were conducted, and blood concentrations were estimated at the time of drug administration and then at 1, 2, and 3 hours after administration. Functional magnetic resonance images were acquired between 1 and 2 hours after administration of the drug. Participants performed a simple visual oddball detection task inside the fMRI scanner.

The paradigm is described in detail elsewhere[31,32] and in the eMethods. A series of arrows was presented on the right or left side of a screen for 600 milliseconds, followed by a blank screen for an average of 1.2 seconds (jittered between 1 and 1.4 seconds, amounting to a total mean intertrial interval of 1.8 seconds). Standard stimuli, presented in 160 trials, were horizontal arrows pointing to the right or left with equal probability. Oddball stimuli, with arrows pointing to the right or left at a 23° angle, were presented in 24 trials that were pseudorandomly interspersed among the standard trials. Participants were instructed to press a right or left button according to the arrow direction for both oddball and standard stimuli. Contrast of the oddball and standard stimuli allowed us to assess the neural response to rareness/deviance (corresponding to stimulus salience), without the potentially confounding effect of other dimensions of stimulus salience, such as targetness, emotional valence, and motivational valence (rewarding or nonrewarding)[37] and to measure the correlates of pure attention allocation to a rare infrequent stimulus.[30,32]

Images were acquired on a 1.5-T system (detailed in the eMethods). Data from the fMRI tasks were analyzed using XBAMv3.4 (http://www.brainmap.it/) (detailed in the eMethods). Images were realigned and smoothed, and the experimental design was convolved with 2 gamma variate functions to model the blood oxygen level–dependent response. Following least-squares fitting of the convolved model to the time series at each voxel, the sum of squares ratio (ratio of model component to residual sum of squares) was determined for the oddball-standard contrast. The significance of the estimated sum of squares values at each voxel was determined using permutation testing.[40] Sum of squares ratio maps for each individual were transformed into standard space,[41] and group activation maps were computed for each drug by determining the median sum of squares ratio at each voxel. Intercondition contrasts were studied using nonparametric repeated-measures analysis of variance,[42] with a voxel-wise threshold of $P = .05$ and the clusterwise threshold set such that the total number of false-positive clusters per brain volume was less than 1; the P value at which the latter occurred is reported herein.

For each drug condition (Δ9-THC, CBD, and placebo), we contrasted the oddball condition with the standard condition. The effects of Δ9-THC and CBD in the whole brain were examined by comparing the activation maps for each drug condition separately with the activation map for the placebo condition. Finally, to test our hypothesis that Δ9-THC and CBD would have opposite effects on activation, we identified areas where the effects of Δ9-THC and CBD relative to the placebo condition were in opposite directions.

Analyses of behavioral data are described in detail in the eMethods. The effects of between-drug differences in symptom levels on activation were examined by correlating measures of activation with the change in the rating from baseline to the mean of those measures at 1 and 2 hours.

RESULTS

PSYCHOPATHOLOGIC EFFECTS

There was a significant effect of drug administration on psychotic symptom ratings (estimated by calculating the area under the curve from baseline to 3 hours) as indexed by the positive symptoms subscale of the Positive and Negative Syndrome Scale[43] ($F_{2,28} = 9.15$, $P = .001$) (eFigure 1). Pairwise comparisons revealed that Δ9-THC significantly increased the severity of psychotic symptoms compared with placebo ($P < .001$) and CBD ($P < .001$),

Table 1. Effect of Δ9-THC and CBD on Task Performance

Characteristic	Accuracy of Responses			*P* Value
	Δ9-THC	Placebo	CBD	
Incorrect responses, %				
Oddball	2.6	1.8	1.4	.16
Standard	2.4	2.3	2.1	.24
Reaction time, mean (SD)				
Oddball	461.9 (134.8)	484.6 (164.7)	468.7 (139.6)	<.001[a] .02[b] .01[c]
Standard	428.5 (112.0)	449.3 (155.3)	439.2 (136.9)	

Abbreviations: CBD, cannabidiol; Δ9-THC, Δ9-tetrahydrocannabinol.
[a] Δ9-Tetrahydrocannabinol vs placebo.
[b] Δ9-Tetrahydrocannabinol vs CBD.
[c] CBD vs placebo.

whereas there was no significant difference between the CBD and placebo conditions ($P>.05$). The effects of Δ9-THC and CBD on other psychopathologic and intoxication measures are reported as supplemental information (eFigure 2). Mean (SD) blood concentrations of Δ9-THC were 3.9 (7.3) and 5.1 (5.6) ng/mL at 1 and 2 hours, respectively (to convert to micromoles per liter, multiply by 3.180), and blood concentrations of CBD were 4.7 (7.0) ng/mL after 1 hour and 17 (29.0) ng/mL after 2 hours.

PERFORMANCE DURING THE VISUAL ODDBALL DETECTION TASK

Reaction Time

As in previous studies,[38] participants took longer to respond to oddball than to standard stimuli across all 3 drug conditions ($P<.001$), independent of the drug condition (**Table 1**). Post hoc pairwise comparisons revealed that response latencies (RTs) were reduced after Δ9-THC relative to both placebo ($P<.001$) and CBD ($P=.02$) across all stimulus conditions. Response latencies after administration of CBD relative to placebo were also significantly reduced across all conditions ($P=.01$). There was a significant interaction ($P=.01$) between drug condition and stimulus (oddball vs standard) on RTs. This was driven by a greater effect ($P=.03$) of Δ9-THC relative to both CBD and placebo on RT during the standard than during the oddball condition; therefore, the difference in RT between the oddball and standard stimuli was greater under the influence of Δ9-THC than it was under the influence of the other drug conditions combined. Thus, although Δ9-THC reduced RTs relative to CBD and placebo in both task conditions, it had a relatively greater effect on RTs to standard stimuli. Conversely, CBD had a greater effect on response latency to oddball than to standard stimuli relative to the placebo condition, but this was not statistically significant ($P>.10$). The order of drug administration (which was counterbalanced across participants) did not have any significant main effect on RTs, and there was no significant interaction between the effects of drug order and drug condition or stimulus type.

Accuracy of Responses

Relative to the placebo condition, responses were less accurate after administration of Δ9-THC than after CBD. However, these differences were not statistically significant.

fMRI RESULTS

Main Effect of the Task (Independent of Drug)

Processing oddball relative to standard stimuli was associated with activation in the left inferior and medial prefrontal cortices, the caudate and putamen, and the parahippocampal gyrus and hippocampus bilaterally, extending to include the amygdala on the right side (eFigure 3). Additional activation was evident in the insula and cerebellum bilaterally and in the thalamus, right inferior parietal lobule, and inferior temporal gyrus.

Effects of Δ9-THC on Activation

Event-related analysis demonstrated that, relative to placebo, Δ9-THC augmented activation in the right inferior, middle, and superior frontal gyri and the right orbitofrontal cortex and frontal pole but attenuated activation in the head of the caudate, putamen, insula, and thalamus on the right side (**Table 2**; **Figure 1**).

Correlation Between Effects of Δ9-THC on Activation, Task Performance, and Psychopathologic Factors

In the right head of the caudate, the effect of Δ9-THC on activation was inversely correlated with the severity of the psychotic symptoms it induced: the more Δ9-THC attenuated the response of the caudate to the oddball-standard contrast, the more severe were the psychotic symptoms ($r=-0.45$; $P=.04$) (**Figure 2**). In this part of the striatum, the effect of Δ9-THC was also inversely correlated ($r=-0.53$; $P=.03$) with its effect on task performance: the greater the attenuation of right caudate activation by Δ9-THC, the greater its effect on the response latency to standard stimuli. There was a significant relationship ($r=0.58$, $P=.04$) observed between the effect

Table 2. Talairach Coordinates of Peak Areas of Activation Under the Influence of Δ9-THC and CBD

Area	Talairach Coordinates x	y	z	Cluster Size, No. of Voxels	*P* Value
Effects of Δ9-THC during the oddball salience task (Δ9-THC > placebo)					
Inferior frontal gyrus	36	44	−7	24	.003
Middle frontal gyrus	40	41	9	9	
Superior frontal gyrus	11	63	15	7	.002
Orbitofrontal cortex	29	52	−13	7	.003
Frontal pole	14	67	4	30	.002
Effects of Δ9-THC during the oddball salience task (Δ9-THC < placebo)					
Caudate head	18	19	4	48	.004
Putamen	25	−4	20		
Insula	43	−7	15	8	.004
Thalamus	25	−22	9	35	.004
Effects of CBD during the oddball salience task (CBD > placebo)[a]					
Caudate body	22	−19	20	8	.02
Parahippocampal gyrus	40	−26	−2	6	.02
Insula	36	11	−2	22	.02
Precentral gyrus	47	−7	9	16	.02
Thalamus	22	−15	15	7	.02
Effects of CBD during the oddball salience task (CBD < placebo)					
Medial prefrontal cortex	−18	33	−7	26	.01
Opposite effects of Δ9-THC and CBD during the oddball salience task (Δ9-THC < placebo < CBD)					
Putamen	−22	0	15	17	
Caudate head and body	−22	26	9	22	.005
	−14	15	9		
Tail of caudate	−22	−33	15	17	.002
Hippocampus	−29	−41	4	18	.002
Parahippocampal gyrus	−29	−41	−2		
Thalamus	−18	−33	4	8	.008
Lingual gyrus	−18	−41	−2	5	.008
Opposite effects of Δ9-THC and CBD during the oddball salience task (Δ9-THC > placebo > CBD)					
Superior frontal gyrus	29	56	−2	32	<.001
	29	56	4		
Middle frontal gyrus	40	48	−13	74	
	40	48	9		
Inferior frontal gyrus	51	26	−13	27	.001
	40	22	−2		
Orbitofrontal cortex	29	30	−18	8	

Abbreviations: CBD, cannabidiol; Δ9-THC, Δ9-tetrahydrocannabinol.
[a] Did not survive correction for less than 1 false-positive cluster.

of Δ9-THC on activation in the right prefrontal cortex and its effects on task performance: the greater the engagement of the right prefrontal cortex under the influence of Δ9-THC, the greater its effects on response latency to standard relative to oddball stimuli. No significant relationship was observed between the effect of Δ9-THC in this region and its effect on psychotic symptoms.

Further post hoc analysis suggested that there was no relationship between the effect of Δ9-THC on response latency to standard relative to oddball trials and its effect on psychotic symptoms.

Effects of CBD on Activation

Cannabidiol attenuated activation in the left medial prefrontal cortex. However, CBD augmented activation in the right caudate, parahippocampal gyrus, insula, precentral gyrus and thalamus, relative to placebo (Table 2).

Direct Comparison of Effects of Δ9-THC and CBD on Activation

Direct contrast revealed that Δ9-THC and CBD had opposite effects on activation in several regions (Table 2; **Figure 3**). In the right superior, middle, inferior, and orbitofrontal gyri, Δ9-THC augmented activation relative to placebo, whereas CBD attenuated activation (Figure 3). Conversely, in the left head, body, and tail of the caudate and in the putamen, parahippocampal gyrus, thalamus, and lingual gyrus, activation was attenuated by Δ9-THC but augmented by CBD.

In the left caudate (x=−22, y=26, z=9 in Talairach space), the effect of Δ9-THC on activation was inversely correlated with the severity of psychotic symptoms that it induced: the more that Δ9-THC attenuated the caudate response to oddball-standard contrast, the more severe were the psychotic symptoms (r=−0.55; P=.02). This correla-

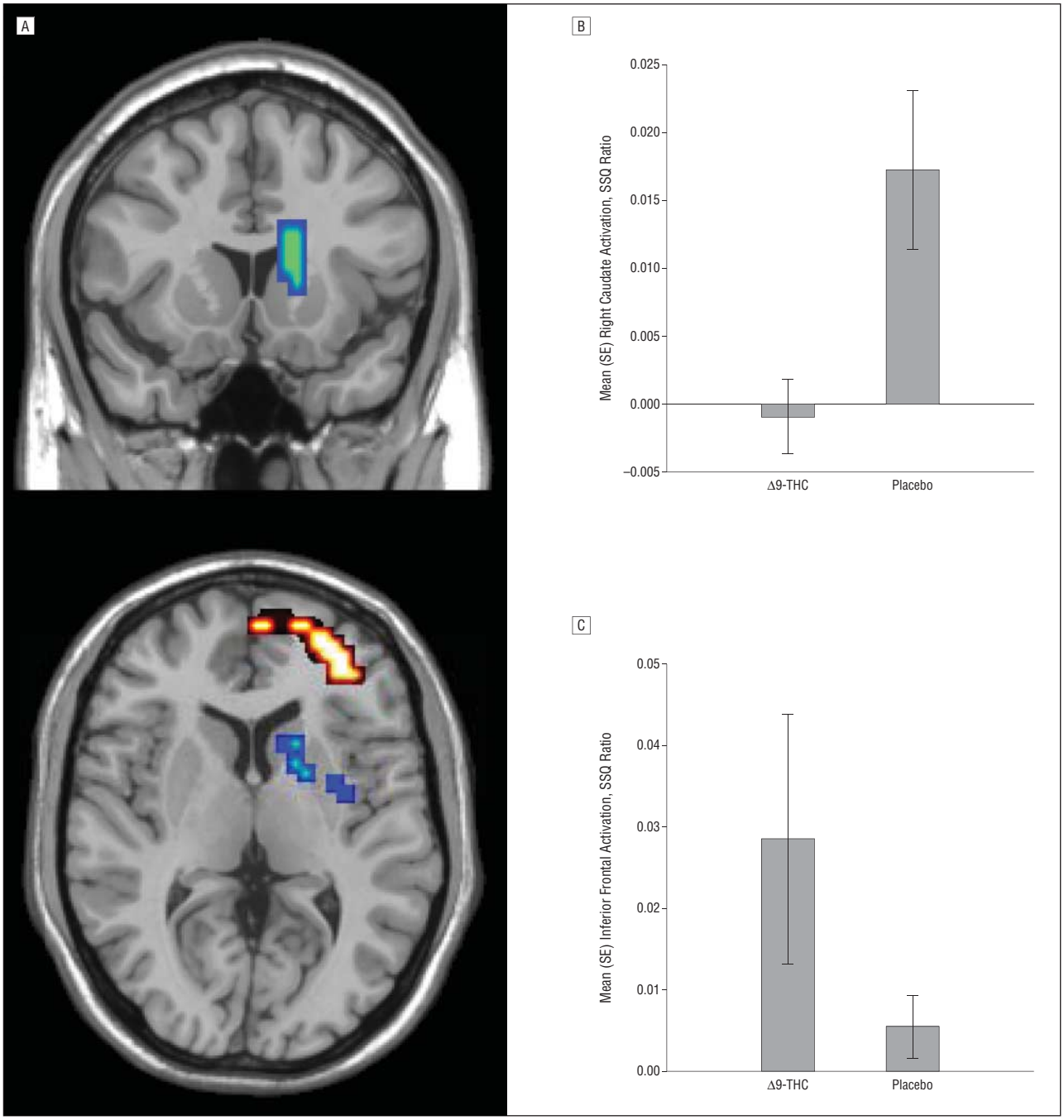

Figure 1. Effect of Δ9-tetrahydrocannabinol (Δ9-THC) relative to placebo on activation (blood oxygen level–dependent response). A, Effect in the right caudate (coronal [top] and transverse [bottom] views) and inferior frontal gyrus (transverse view [bottom]) during visual oddball salience processing. The left side of the brain is shown on the left side of the images. B, Activation in the caudate in part A was attenuated by Δ9-THC relative to the placebo condition. C, Inferior frontal activation in part A was augmented by Δ9-THC relative to the placebo condition. Magnitude of activation is indexed by the mean sum of squares (SSQ) ratio. Data are given in arbitrary units.

tion became stronger after excluding an outlier identified using Cook's D reliability analysis ($r=-0.72$; $P=.002$). This relationship between psychotic symptoms and activation was specific to the left caudate and was not observed in the left parahippocampal or prefrontal clusters. The effect of Δ9-THC in this part of the caudate was also inversely correlated ($r=-0.66$; $P=.02$) with its effect on task performance: the greater the attenuation of left caudate activation by Δ9-THC, the greater its effect on the response latency to standard relative to oddball stimuli.

COMMENT

We investigated the effects of Δ9-THC and CBD on the neural substrate of attentional salience processing. Consistent with our first hypothesis, that Δ9-THC would perturb salience processing, Δ9-THC had a greater effect than placebo on the reaction time to standard (nonsalient) relative to oddball (salient) stimuli. Moreover, Δ9-THC modulated both prefrontal and striatal function during the task,

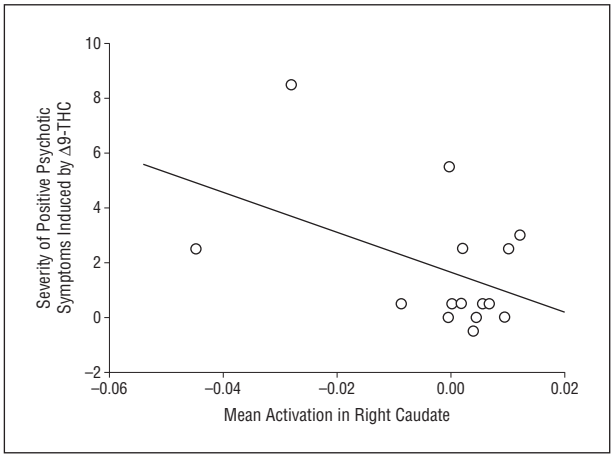

Figure 2. Correlation between the effect of Δ9-tetrahydrocannabinol (Δ9-THC) on activation in the right caudate (*x*-axis with arbitrary units) and the severity of psychotic symptoms (indexed by the score on the positive symptoms subscale of the Positive and Negative Symptom Scale) concurrently induced by it.

augmenting activation in the former region and attenuating it in the latter. Our second hypothesis was that the effect of Δ9-THC on psychotic symptoms would be related to its influence on striatal activation. The data were consistent with this hypothesis, with a significant correlation between its striatal and symptomatic effects. Finally, in line with our third hypothesis, CBD had effects opposite to those of Δ9-THC on activation in the striatum, prefrontal cortex, and medial temporal cortex.

EFFECTS OF Δ9-THC ON TASK PERFORMANCE AND PSYCHOTIC SYMPTOMS

The responses to all task stimuli were faster under the influence of Δ9-THC than placebo. Similar effects of Δ9-THC on reaction times during a range of other tasks have been reported in some[44,45] but not all[45-47] studies. However, its effect on response time was more marked for standard than for oddball stimuli, suggesting that Δ9-THC may have made the nonsalient stimuli appear to be relatively salient. It is possible that the effect of Δ9-THC on response time was stronger for standard stimuli because this condition was studied using more trials than its oddball counterpart, thus providing greater statistical power to detect a drug effect. Nevertheless, had this been the explanation, the same might have applied to the effect of CBD on response times to standard and oddball stimuli, and this was not the case. Another possibility is that, under the influence of Δ9-THC, there was a nonspecific disinhibition of psychomotor responses, resulting in a general speeding of responses to stimuli, and that this was more prominent with standard than with oddball stimuli, as the former condition was less demanding. However, when the same participants were studied in the same scanning session while performing a different task that required a button-press response to indicate the sex of persons when viewing their faces, Δ9-THC did not reduce the RTs (data not shown).

Previous work[48] involving ketamine-induced psychotic symptoms suggests that the relationship between psychotic symptoms and alteration in the processing of salience of environmental stimuli may involve an attenuation of the salience of unpredictable salient stimuli, as well as enhanced salience of predictable nonsalient stimuli. In the present study, although Δ9-THC was associated with a reduction in the RTs to standard stimuli but not with an increase in the RTs to oddball stimuli, it did have effects on the neural response to both salient and nonsalient stimuli (discussed further in the next subsection, "Neural Effects of Δ9-THC"). The absence of an effect on responses to salient stimuli at the behavioral level may reflect a lesser sensitivity of behavioral compared with physiological measures.

The effects of Δ9-THC on the processing of nonsalient stimuli are of particular interest in relation to its effects on psychosis. An increased responsiveness to stimuli that are not normally salient may be fundamental to the development of psychotic symptoms.[6] Moreover, in the present study, the magnitude of Δ9-THC's effect on response times to nonsalient stimuli was correlated with its effect on activation in the right caudate, the region where the physiological effect of Δ9-THC was linked to its induction of psychotic symptoms. However, a direct relationship between the effect of Δ9-THC on response times to nonsalient stimuli and its induction of psychotic symptoms was not observed. Nevertheless, the present study was powered to detect the effects of the drug on the blood oxygen level–dependent response and may have lacked sufficient power to detect a relationship between drug effects at the behavioral level. Independent evidence indicates that the striatum plays a central role in normal salience processing,[38,49] as well as in the aberrant processing of salience in individuals with psychotic symptoms.[8] Our results are also in line with evidence that, under the influence of Δ9-THC, irrelevant background sounds and visual patterns became more salient during the performance of a visual processing task[47] and that people with long-term cannabis use show impairments in filtering out nonsalient information.[50]

NEURAL EFFECTS OF Δ9-THC

Δ9-Tetrahydrocannabinol modulated brain activation in areas that normally respond to salient stimuli, including the right inferior prefrontal cortex[30,51-53] and the right caudate.[37,38] Δ9-Tetrahydrocannabinol reduced the caudate response to oddball stimuli but augmented the prefrontal response. In the right caudate, effect of Δ9-THC reflected augmentation of activation while viewing standard stimuli, as well as attenuation of activation while viewing salient oddball stimuli, resulting in a net reduction in the difference between the caudate response to oddball relative to standard stimuli. As discussed in the "Effects of Δ9-THC on Task Performance and Psychotic Symptoms" subsection, this effect of Δ9-THC was correlated with its effect on speeding of the response to the standard stimuli and inducing psychotic symptoms. In the prefrontal cortex, Δ9-THC augmented the response to oddball relative to standard stimuli. Greater activation of the prefrontal cortex to nonsalient stimuli and a reduced response to salient stimuli have been reported[48] as acute effects of ketamine, another drug that can induce psychotic symptoms. In individuals at ultrahigh risk of developing psychosis relative to healthy control persons, the erroneous perception of nonsalient

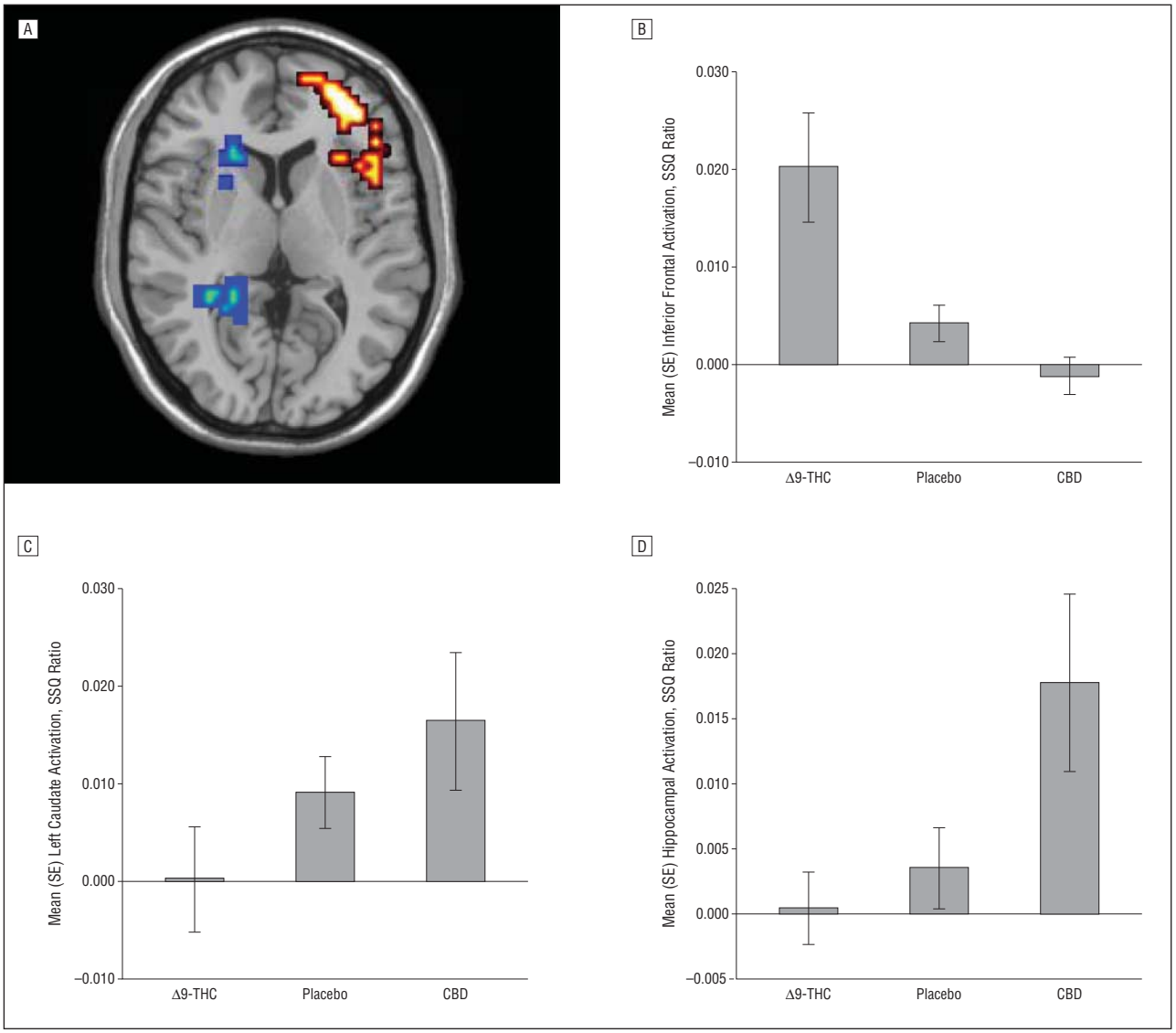

Figure 3. Effects of Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and placebo. A, Opposite effects of Δ9-THC and CBD relative to placebo on prefrontal, left caudate, and hippocampal activation (blood oxygen level–dependent response) during visual oddball salience processing. The left side of the brain is shown on the left side of the image. B, Prefrontal activation in part A was augmented by Δ9-THC but attenuated by CBD. C, Caudate activation in part A was attenuated by Δ9-THC but augmented by CBD. D, Hippocampal activation (A) was attenuated by Δ9-THC but augmented by CBD. Magnitude of activation is indexed by the mean sum of squares (SSQ) ratio. Data are given in arbitrary units.

stimuli as salient is associated with increased prefrontal cortical activation.[54] An effect of Δ9-THC on prefrontal activation in the context of salience processing is thus consistent with data from previous studies. Findings in this region are particularly interesting in relation to our findings in the striatum, which plays a central role in salience processing and is strongly connected to the prefrontal cortex.[55] Altered prefrontal-striatal interactions are thought to be critical in the pathophysiologic characteristics of psychosis.[56] However, Δ9-THC augmented the prefrontal response to salient (oddball) as opposed to nonsalient (standard) stimuli, which seems at odds with the previous findings. The direction of the prefrontal effect is difficult to interpret but could reflect a compensatory response to the effect of Δ9-THC on striatal activation, where it had an attenuating effect. Δ9-Tetrahydrocannabinol increased reaction times to oddball stimuli, and its augmentation of the prefrontal response was correlated with this effect. This suggests that the greater prefrontal response during the oddball condition was related to the speeding of the reactions to oddball stimuli with Δ9-THC, perhaps because this was associated with an increase in task demands. In studies involving actual driving and simulator driving tasks, cautious driving behavior characterized by driving at reduced speeds and with greater headway has been reported in individuals under the influence of Δ9-THC, reflecting a similar compensatory effect.[57-60]

Collectively, these observations suggest that Δ9-THC may increase the aberrant attribution of salience and induce psychotic symptoms through its effects on the striatum and lateral prefrontal cortex. This is consistent with evidence that striatal[8,9,61] and lateral prefrontal[48,54] function are altered during salience processing in patients with psychosis,[8,9,61] individuals at ultrahigh risk of psychosis,[54] and persons in a drug-induced psychotic state.[48] The precise neurochemical mechanisms underlying these ef-

fects of Δ9-THC are unclear. However, administration of Δ9-THC alters central dopamine transmission in humans,[10,62] and perturbed dopamine function is thought to be a key factor in the inappropriate attribution of salience to environmental stimuli or events.[63,64] Contemporary models of psychosis propose that dopamine dysfunction leads to the development of psychotic symptoms through an effect on salience processing.[6] Thus, it is possible that administration of Δ9-THC perturbed salience processing and induced psychotic symptoms through its effects on central dopamine function.

OPPOSITE EFFECTS OF Δ9-THC AND CBD

Cannabidiol augmented the response of the right caudate to the task relative to placebo, although this did not survive the conservative threshold of less than 1 false-positive cluster. However, when the effects of CBD were contrasted with those of Δ9-THC and placebo, there was a significant effect in the left caudate, with CBD augmenting, but Δ9-THC attenuating, the response. At the behavioral level, there was a trend for CBD to have a greater effect on the speeding of the response latency for oddball relative to standard stimuli. These effects suggest that CBD may also influence the effect of cannabis use on salience processing—and hence psychotic symptoms—by having an opposite effect, enhancing the appropriate response to salient stimuli. This is consistent with evidence that CBD has behavioral[16-18,20,24,25,65] and neurophysiological[20] effects opposite to those of Δ9-THC and that CBD may have therapeutic potential as an antipsychotic.[23-25]

RELATIONSHIP BETWEEN THE EFFECTS OF Δ9-THC ON ACTIVATION AND ON SYMPTOMS AND TASK PERFORMANCE

There was a significant relationship between the effects of Δ9-THC on activation and its effects on task performance and positive psychotic symptoms in the right and left dorsal striatum. In the right dorsal striatum, this relationship was in the region where Δ9-THC attenuated activation relative to placebo. The relationship in the left dorsal striatum was in the region where the effects of Δ9-THC were opposite from those of CBD. These relationships were observed in roughly homotopic areas of the dorsal striatum in the 2 cerebral hemispheres. This suggests that the relationship between the effects of Δ9-THC on activation and its effects on task performance and positive psychotic symptoms is not a chance finding, as we found the same pattern of correlations in 2 similar striatal regions. The relationship between the effects of Δ9-THC on activation and its effect on task performance and positive psychotic symptoms presented herein is also consistent with evidence linking the effects of Δ9-THC on psychotic symptoms and the striatum[20] and evidence linking the striatum, dopamine dysfunction, and psychosis.[66]

LIMITATIONS

In neuroimaging studies that involve pharmacologic challenges, it is difficult to exclude the possibility that the drug's effects reflect an influence on cerebral blood flow rather than neural activity. However, studies[67] in rodents have shown that administration of Δ9-THC reduces glucose metabolism in the striatum, indicating that the drug has a direct effect on neural activity. In humans, long-term cannabis use does not affect neurovascular coupling or the hemodynamic response measured with fMRI,[68] and acute challenge with other drugs that have vascular effects does not alter the shape of the hemodynamic response that is used to estimate effects in fMRI studies. This is consistent with other evidence[69,70] that fMRI can reliably estimate drug-induced changes in neural activity, even for drugs that affect the cerebral vasculature. Previous studies have not found effects of Δ9-THC on global cerebral blood flow[71] or on regional blood flow in the striatum during cognitive tasks.[72,73]

The volunteers who participated in the present study were also assessed while performing an emotional processing task, the results of which are reported elsewhere.[22] During the emotional processing task, Δ9-THC attenuated activation in the inferior frontal gyrus, whereas, during the oddball task in the present study, Δ9-THC increased activation in the same region. Similarly, CBD attenuated parahippocampal activation during the fear processing task but increased engagement of the same region during the oddball task. If these effects of Δ9-THC and CBD had been due to their influence on the vascular supply to these regions, the same drugs would have to have had opposite effects on blood flow to the same region in the same individuals within the same scanning session. This seems very unlikely. Moreover, the drug effects were in regions where similar effects have been reported in electrophysiologic studies,[74,75] which were independent of vascular effects.

Another possibility is that changes in the level of CBD in blood during a single scanning session may have affected the results presented herein. The task described was part of a larger battery of fMRI activation paradigms that were administered during the study. They were always presented in the same order across the different study sessions. As a result, activation during the tasks performed later in the scanning session might have been modulated to a greater extent by CBD than were those performed earlier. Although this modulation might have influenced the relative effects of CBD on the different cognitive tasks used in the study, CBD would have affected the task we describe in the same manner for all participants, since the same order of tasks was repeated across all participants and all drug conditions. Hence, it would not have affected the differences between the effects of Δ9-THC and CBD on activation during the task presented herein.

In conclusion, these data provide the first evidence, to our knowledge, that the effects of cannabis on psychosis may be mediated by influencing the neural substrate of attentional salience processing. They also provide experimental support for the salience model of psychosis, which proposes that psychotic symptoms develop through the inappropriate attribution of salience to nonsalient stimuli.[6]

Submitted for Publication: June 8, 2011; accepted July 28, 2011.

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Author Contributions: Dr Bhattacharyya had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: None reported.
Funding/Support: This work was supported by a Joint Medical Research Council/Priory Clinical research training fellowship from the Medical Research Council, United Kingdom, to Dr Bhattacharyya and a grant from the Psychiatry Research Trust, United Kingdom. Dr Crippa is the recipient of a Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil) productivity fellowship.
Role of the Sponsors: The study sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The eAppendix and eFigures are available at http://www.archgenpsychiatry.com.
Additional Contributions: Glynis Ivin, BPharm, provided assistance with the masking procedure, as well as with storage and dispensing of the drugs, and Mitul Mehta, PhD, provided helpful comments on the manuscript.

REFERENCES

1. Hall W, Solowij N. Adverse effects of cannabis. *Lancet*. 1998;352(9140):1611-1616.
2. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, Allen P, Seal ML, Fletcher PC, Crippa JA, Giampietro V, Mechelli A, Atakan Z, McGuire P. Modulation of mediotemporal and ventrostriatal function in humans by Δ9-tetrahydrocannabinol: a neural basis for the effects of *Cannabis sativa* on learning and psychosis. *Arch Gen Psychiatry*. 2009;66(4):442-451.
3. Dsouza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry*. 2005;57(6):594-608.
4. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370(9584):319-328.
5. Guillin O, Abi-Dargham A, Laruelle M. Neurobiology of dopamine in schizophrenia. *Int Rev Neurobiol*. 2007;78:1-39.
6. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160(1):13-23.
7. Roiser JP, Stephan KE, den Ouden HE, Barnes TR, Friston KJ, Joyce EM. Do patients with schizophrenia exhibit aberrant salience? *Psychol Med*. 2009;39(2):199-209.
8. Jensen J, Willeit M, Zipursky RB, Savina I, Smith AJ, Menon M, Crawley AP, Kapur S. The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology*. 2008;33(3):473-479.
9. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, Jones PB, Bullmore ET, Robbins TW, Fletcher PC. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 2008;13(3):239, 267-276.
10. Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, van Gerven JM, Ramsey NF, Lammertsma AA, Kahn RS. Δ9-Tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology*. 2009;34(3):759-766.
11. Tart CT. Marijuana intoxication common experiences. *Nature*. 1970;226(5247):701-704.
12. Berke M. *The Cannabis Experience: An Interpretative Study of the Effects of Marijuana and Hashish*. London, England: Peter Owen; 1974.
13. Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H. Comparison of the subjective effects of Δ^9-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology (Berl)*. 2002;161(4):331-339.
14. Green B, Kavanagh D, Young R. Being stoned: a review of self-reported cannabis effects. *Drug Alcohol Rev*. 2003;22(4):453-460.
15. Laviolette SR, Grace AA. Cannabinoids potentiate emotional learning plasticity in neurons of the medial prefrontal cortex through basolateral amygdala inputs. *J Neurosci*. 2006;26(24):6458-6468.
16. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of Δ^9-tetrahydrocannabinol in man. *Eur J Pharmacol*. 1974;28(1):172-177.
17. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther*. 1976;19(3):300-309.
18. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by Δ9-THC in normal subjects. *Psychopharmacology (Berl)*. 1982;76(3):245-250.
19. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199-215.
20. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35(3):764-774.
21. Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29(2):417-426.
22. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK. Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry*. 2009;66(1):95-105.
23. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a *Cannabis sativa* constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39(4):421-429.
24. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*. 2008;30(3):271-280.
25. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry*. 2008;192(4):306-307.
26. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Δ9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*. 2010;35(9):1879-1885.
27. Solinas M, Panlilio LV, Tanda G, Makriyannis A, Matthews SA, Goldberg SR. Cannabinoid agonists but not inhibitors of endogenous cannabinoid transport or metabolism enhance the reinforcing efficacy of heroin in rats. *Neuropsychopharmacology*. 2005;30(11):2046-2057.
28. Solinas M, Panlilio LV, Goldberg SR. Exposure to Δ-9-tetrahydrocannabinol (THC) increases subsequent heroin taking but not heroin's reinforcing efficacy: a self-administration study in rats. *Neuropsychopharmacology*. 2004;29(7):1301-1311.
29. Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *J Neurosci*. 2009;29(47):14764-14769.

30. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356.
31. Rubia K, Smith AB, Brammer MJ, Taylor E. Temporal lobe dysfunction in medication-naïve boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biol Psychiatry*. 2007;62(9):999-1006.
32. Rubia K, Hyde Z, Halari R, Giampietro V, Smith A. Effects of age and sex on developmental neural networks of visual-spatial attention allocation. *Neuroimage*. 2010;51(2):817-827.
33. Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science*. 1980;210(4471):803-805.
34. Strange BA, Dolan RJ. Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus*. 2001;11(6):690-698.
35. Düzel E, Habib R, Rotte M, Guderian S, Tulving E, Heinze HJ. Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. *J Neurosci*. 2003;23(28):9439-9444.
36. Crottaz-Herbette S, Lau KM, Glover GH, Menon V. Hippocampal involvement in detection of deviant auditory and visual stimuli. *Hippocampus*. 2005;15(1):132-139.
37. Bunzeck N, Düzel E. Absolute coding of stimulus novelty in the human substantia nigra/VTA. *Neuron*. 2006;51(3):369-379.
38. Zink CF, Pagnoni G, Martin ME, Dhamala M, Berns GS. Human striatal response to salient nonrewarding stimuli. *J Neurosci*. 2003;23(22):8092-8097.
39. Nelson HE. *National Adult Reading Test (NART): Test Manual*. Windsor, England: NFER- Nelson; 1982.
40. Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, Carpenter TA, Brammer M. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. *Hum Brain Mapp*. 2001;12(2):61-78.
41. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme Medical; 1988.
42. Brammer MJ, Bullmore ET, Simmons A, Williams SC, Grasby PM, Howard RJ, Woodruff PW, Rabe-Hesketh S. Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magn Reson Imaging*. 1997;15(7):763-770.
43. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.
44. Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain*. 2006;129(pt 5):1096-1112.
45. Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)*. 2002;164(1):61-70.
46. Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25(5):757-765.
47. Dsouza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29(8):1558-1572.
48. Corlett PR, Honey GD, Aitken MR, Dickinson A, Shanks DR, Absalom AR, Lee M, Pomarol-Clotet E, Murray GK, McKenna PJ, Robbins TW, Bullmore ET, Fletcher PC. Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: linking cognition, brain activity, and psychosis. *Arch Gen Psychiatry*. 2006;63(6):611-621.
49. Zink CF, Pagnoni G, Chappelow J, Martin-Skurski M, Berns GS. Human striatal activation reflects degree of stimulus saliency. *Neuroimage*. 2006;29(3):977-983.
50. Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharmacol Biochem Behav*. 1991;40(3):683-688.
51. Downar J, Crawley AP, Mikulis DJ, Davis KD. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J Neurophysiol*. 2002;87(1):615-620.
52. Kiehl KA, Liddle PF. An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. *Schizophr Res*. 2001;48(2-3):159-171.
53. Menon V, White CD, Eliez S, Glover GH, Reiss AL. Analysis of a distributed neural system involved in spatial information, novelty, and memory processing. *Hum Brain Mapp*. 2000;11(2):117-129.
54. Roiser J. Aberrant salience in subjects at high risk of psychosis related to altered dorsolateral prefrontal function. *Schizophr Res*. 2010;117(2-3):168. doi: 10.1016/j.schres.2010.02.191.
55. McGuire PK, Bates JF, Goldman-Rakic PS. Interhemispheric integration, II: symmetry and convergence of the corticostriatal projections of the left and the right principal sulcus (PS) and the left and the right supplementary motor area (SMA) of the rhesus monkey. *Cereb Cortex*. 1991;1(5):408-417.
56. Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. 2007;362(1481):917-932.
57. Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. *Drug Alcohol Depend*. 2004;73(2):109-119.
58. Robbe HWJ. *Influence of Marijuana on Driving*. Maastricht, the Netherlands: Institute for Human Psychopharmacology, University of Limburg; 1994.
59. Sexton BF, Tunbridge RJ, Brook-Carter N, Jackson PG, Wright K, Stark MM, Englehart K. *The Influence of Cannabis on Driving: A Report Prepared for the UK Department of the Environment, Transport and the Regions (Road Safety Division)*. Crowthorne, Berkshire: TRL Ltd; 2000.
60. Smiley A. *On Road and Driving Simulator Studies*. Rev and expanded ed. Toronto, ON: Addiction Research Foundation; 1999.
61. Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wüstenberg T, Villringer A, Knutson B, Kienast T, Gallinat J, Wrase J, Heinz A. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology (Berl)*. 2006;187(2):222-228.
62. Stokes PR, Egerton A, Watson B, Reid A, Breen G, Lingford-Hughes A, Nutt DJ, Mehta MA. Significant decreases in frontal and temporal ^{11C}-raclopride binding after THC challenge. *Neuroimage*. 2010;52(4):1521-1527.
63. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)*. 2007;191(3):391-431.
64. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005;79(1):59-68.
65. Malone DT, Jongejan D, Taylor DA. Cannabidiol reverses the reduction in social interaction produced by low dose Δ^9-tetrahydrocannabinol in rats. *Pharmacol Biochem Behav*. 2009;93(2):91-96.
66. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;35(3):549-562.
67. Freedland CS, Whitlow CT, Miller MD, Porrino LJ. Dose-dependent effects of Δ^9-tetrahydrocannabinol on rates of local cerebral glucose utilization in rat. *Synapse*. 2002;45(2):134-142.
68. Murphy K, Dixon V, LaGrave K, Kaufman J, Risinger R, Bloom A, Garavan H. A validation of event-related FMRI comparisons between users of cocaine, nicotine, or cannabis and control subjects. *Am J Psychiatry*. 2006;163(7):1245-1251.
69. Luo F, Wu G, Li Z, Li SJ. Characterization of effects of mean arterial blood pressure induced by cocaine and cocaine methiodide on BOLD signals in rat brain. *Magn Reson Med*. 2003;49(2):264-270.
70. Gollub RL, Breiter HC, Kantor H, Kennedy D, Gastfriend D, Mathew RT, Makris N, Guimaraes A, Riorden J, Campbell T, Foley M, Hyman SE, Rosen B, Weiskoff R. Cocaine decreases cortical cerebral blood flow but does not obscure regional activation in functional magnetic resonance imaging in human subjects. *J Cereb Blood Flow Metab*. 1998;18(7):724-734.
71. Ponto LL, O'Leary DS, Koeppel J, Block RI, Watkins GL, Richmond JC, Ward CA, Clermont DA, Schmitt BA, Hichwa RD. Effect of acute marijuana on cardiovascular function and central nervous system pharmacokinetics of [^{15}O]water: effect in occasional and chronic users. *J Clin Pharmacol*. 2004;44(7):751-766.
72. O'Leary DS, Block RI, Flaum M, Schultz SK, Boles Ponto LL, Watkins GL, Hurtig RR, Andreasen NC, Hichwa RD. Acute marijuana effects on rCBF and cognition: a PET study. *Neuroreport*. 2000;11(17):3835-3841.
73. O'Leary DS, Block RI, Koeppel JA, Flaum M, Schultz SK, Andreasen NC, Ponto LB, Watkins GL, Hurtig RR, Hichwa RD. Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology*. 2002;26(6):802-816.
74. Morrison PD, Nottage J, Stone JM, Bhattacharyya S, Tunstall N, Brenneisen R, Holt D, Wilson D, Sumich A, McGuire P, Murray RM, Kapur S, Ffytche DH. Disruption of frontal theta coherence by Δ^9-tetrahydrocannabinol is associated with positive psychotic symptoms. *Neuropsychopharmacology*. 2011;36(4):827-836.
75. Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM. Effects of acute oral Δ^9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. *Eur Neuropsychopharmacol*. 2008;18(8):569-577.