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Increased hippocampal engagement during learning as a marker of sensitivity to psychotomimetic effects of δ-9-THC

Sagnik Bhattacharyya[1], Thomas Sainsbury[1,2], Paul Allen[3], Chiara Nosarti[1,4], Zerrin Atakan[1], Vincent Giampietro[5], Michael Brammer[5] and P K McGuire[1]

[1]Department of Psychosis Studies, King's College London, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, UK; [2]Centre for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE1 1UL, UK; [3]Department of Psychology, University of Roehampton, UK; [4]Centre for the Developing Brain, Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK and [5]Department of Neuroimaging, King's College London, Institute of Psychiatry, PO Box 089, De Crespigny Park, London, SE5 8AF, UK

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Author for correspondence:
Dr Sagnik Bhattacharyya, E-mail: sagnik.2.bhattacharyya@kcl.ac.uk

Abstract

Background. Cannabis and its main psychoactive ingredient δ-9-tetrahydrocannibidiol (THC) can induce transient psychotic symptoms in healthy individuals and exacerbate them in those with established psychosis. However, not everyone experience these effects, suggesting that certain individuals are particularly susceptible. The neural basis of this sensitivity to the psychotomimetic effects of THC is unclear.

Methods. We investigated whether individuals who are sensitive to the psychotomimetic effects of THC (TP) under experimental conditions would show differential hippocampal activation compared with those who are not (NP). We studied 36 healthy males under identical conditions under the influence of placebo or THC (10 mg) given orally, on two separate occasions, in a pseudo-randomized, double-blind, repeated measures, within-subject, cross-over design, using psychopathological assessments and functional MRI while they performed a verbal learning task. They were classified into those who experienced transient psychotic symptoms (TP; $n = 14$) following THC administration and those who did not (NP; $n = 22$).

Results. Under placebo conditions, there was significantly greater engagement of the left hippocampus ($p < 0.001$) in the TP group compared with the NP group during verbal encoding, which survived leave-one-out analysis. The level of hippocampal activation was directly correlated (Spearman's $\rho = 0.44$, $p = 0.008$) with the severity of transient psychotic symptoms induced by THC. This difference was not present when we compared two subgroups from the same sample that were defined by sensitivity to anxiogenic effects of THC.

Conclusions. These results suggest that altered hippocampal activation during verbal encoding may serve as a marker of sensitivity to the acute psychotomimetic effects of THC.

Introduction

Regular cannabis use is associated with a dose-dependent increase in the risk of onset (Zammit *et al.* 2002; Moore *et al.* 2007) and exacerbation (Patel *et al.* 2016; Schoeler *et al.* 2016*b*, *c*, *d*) of psychotic disorders such as schizophrenia. Consistent with this, δ-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, has been shown in experimental studies to induce transient psychotic symptoms in healthy subjects (D'Souza *et al.* 2004; Bhattacharyya *et al.* 2009; Morrison *et al.* 2011; Bhattacharyya *et al.* 2015*a*) and exacerbate them in schizophrenia patients (D'Souza *et al.* 2005; Henquet *et al.* 2006).

However, there is a marked variation in the psychotomimetic and cognitive effects of cannabis based on genetic (Bhattacharyya *et al.* 2012*a*; Bhattacharyya *et al.* 2014) and personality and familial factors (McGuire *et al.* 1995; Henquet *et al.* 2005; Stirling *et al.* 2008; van Winkel *et al.* 2011; Di Forti *et al.* 2012) as well as the composition of cannabis (Bhattacharyya *et al.* 2010). Experimental studies in healthy individuals suggest that even when given substantial doses of pure THC, not all will experience a state of transient psychosis (Bhattacharyya *et al.* 2010; Atakan *et al.* 2013). While this may point towards fundamental neurobiological differences between those who are susceptible to the psychotomimetic effects of THC and those who are not, it is unclear if this is the case.

Evidence from animal models has led to the hypothesis that the development of psychosis may be associated with an increased hippocampal activity (Lodge & Grace, 2007), in turn driving striatal dopaminergic overactivity (Lodge & Grace, 2011). This is consistent with evidence of increased resting hippocampal regional cerebral blood flow (Allen *et al.* 2016) and increased hippocampal activation during memory tasks (Valli *et al.* 2011) in individuals at high risk of

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developing psychosis (Allen *et al.* 2016). The hippocampus has a central role in memory formation and relational memory binding (Hannula & Ranganath, 2008). Patients with schizophrenia have a deficit in verbal learning and memory (Hannula & Ranganath, 2008; Schaefer *et al.* 2013; Lepage *et al.* 2015) and altered hippocampal function during memory processing (Hannula & Ranganath, 2008; Ragland *et al.* 2015), leading to the suggestion that memory deficits and associated altered brain function may be potential neurocognitive markers of schizophrenia (Lepage *et al.* 2015). Impairment in learning and memory, specifically dose-related (Curran *et al.* 2002) impairment in verbal learning (Curran *et al.* 2002; Henquet *et al.* 2006; Ranganathan & D'Souza, 2006) that cannot be accounted for by effects on attention (Curran *et al.* 2002; Ranganathan & D'Souza, 2006), is also one of the most prominent acute cognitive effects of THC in man that persists in chronic users (Solowij *et al.* 2002; Schoeler & Bhattacharyya, 2013; Schoeler *et al.* 2016*a*). Patients with schizophrenia are more vulnerable to dose-related verbal learning impairments under the influence of THC compared with healthy individuals (D'Souza *et al.* 2005). The hippocampus has a high density of the type 1 central cannabinoid receptors (Elphick & Egertova, 2001; Eggan & Lewis, 2007), which are the main central target of THC and animal studies show that the effect of THC on learning correlate with its effect on hippocampal neuronal firing (Heyser *et al.* 1993; Robbe *et al.* 2006). Hence, one may predict that increased hippocampal activity may also underlie sensitivity to the psychotomimetic effects of THC. This hypothesis has not been tested before. The only previous study that investigated neurophysiological differences between those who develop transient psychotic symptoms (TP group) and those that do not (NP group) in response to experimental THC challenge employed a cognitive (psychomotor control) task that does not normally engage the hippocampal region (Atakan *et al.* 2013).

On the other hand, neuroimaging studies in healthy individuals have demonstrated that THC disrupts brain activity in regions associated with memory such as the medial temporal and prefrontal cortices as well as functional connectivity between them during memory processing (Bhattacharyya *et al.* 2009; 2012*a*; 2015*b*) and other cognitive tasks (Bhattacharyya *et al.* 2010, 2012*b*, 2015*b*). In the present study, we therefore re-analysed previously reported data acquired employing a verbal memory paradigm that engages the hippocampus (Bhattacharyya *et al.* 2012*a*) to examine whether differences in brain activation during task performance would differentiate those healthy individuals who experience transient psychotic (TP) symptoms from those who do not (NP), following an acute challenge with THC. Brain activation was indexed using blood oxygen level-dependent (BOLD) haemodynamic response measured using functional MRI (fMRI) while participants performed a verbal paired associates learning task. We predicted that when performing the task under placebo conditions, individuals who were sensitive to the psychotomimetic effects of THC (TP PLB) would show greater hippocampal activation than those who were not (NP PLB). We then tested the hypothesis that this difference in brain activation under the placebo condition between TP and NP groups would be directly associated with the magnitude of THC-induced psychotomimetic effects in the same individuals. Finally, we hypothesized that THC administration would modulate brain activation differently in the TP and NP groups, reflecting the different symptomatic effects.

Furthermore, we carried out exploratory analysis to investigate whether the difference in neurophysiological response between TP and NP under placebo condition was a specific biomarker for THC-induced psychotomimetic effects as opposed to the acute effects of THC on other symptoms such as anxiety (Bhattacharyya *et al.* 2017), by testing whether brain activity differences between individuals who experienced acute anxiety (TA PLB) under THC *v.* those who did not experience anxiety (NA PLB) were in different brain regions compared with differences between the 'TP PLB' and 'NP PLB' groups.

Methods and materials

Using an established protocol (Bhattacharyya *et al.* 2009, 2012*a*, *b*), 36 healthy, occasional cannabis user male participants attended two sessions at least 1 month apart when they were given an identical capsule to be taken orally, containing either 10 mg of THC or placebo using a pseudo-randomized, double-blind, repeated-measures, within-subject, cross-over design and a counterbalanced order of drug administration. Following administration, the subjects were required to complete a verbal paired associate learning task (Bhattacharyya *et al.* 2009) while their brain activity was measured using fMRI. Methods and study participants are described in detail in Supplementary Methods. While we have previously reported the effects of THC and its genetic moderation at a group level (Bhattacharyya *et al.* 2009, 2012*a*), the present study focuses on brain function differences between those individuals who were sensitive to the psychotomimetic effects of THC compared with those who were not (see details below).

Participants were right-handed, English-speaking males, without a personal or family history of mental illness in first-degree relatives, mean age of 25.97 ± 5.58 and mean National Adult Reading Test (NART) score of 97.7 ± 6. Alcohol, cannabis and other illicit drug use was assessed using the Addiction Severity Index (McLellan *et al.* 1980). They had used cannabis upto 25 times in their lifetime, drank <21 units/week of alcohol and had minimal exposure to other illicit drugs (see online Supplementary Table S1). Participants were asked to abstain from all recreational drugs for the duration of the study and 1 month prior to it. Each participant passed a negative urine drug screen on the morning of each session for opiates, cocaine, amphetamines, benzodiazepines and THC to ensure that no traces of these drugs were in their systems. Psychological assessments (to assess mental state) were conducted and blood samples (to assess drug levels) were taken prior to and 1, 2, and 3 h after drug administration. MRI scans were performed 1 h after ingestion of the drug.

Psychotomimetic effects of THC were measured by an experienced clinical researcher using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). State-Trait Anxiety Inventory-State (STAI) (Spielberger, 1983) and the Analogue Intoxication Scale (AIS) (Mathew *et al.* 1992) were used to measure anxiety and level of intoxication, respectively. Psychological effects peaked 2 h after THC administration, and hence ratings at this time point were used to compare the TP and NP groups.

Classification of participants on the basis of sensitivity to THC

For the purpose of this investigation, we established *a priori* criteria (also see Supplementary Methods) to define transient psychosis induced by THC, which were used to classify the participants into those who experienced transient psychotomimetic effects (TP) and those who did not (NP). Participants were identified

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as having experienced transient psychotic symptoms and allocated to the TP group if they scored at least 3 or more on any of the PANSS-positive subscale items that measured psychotic symptoms (delusions, hallucinations, suspiciousness/persecution) during any of the time points when ratings were obtained following THC administration (Atakan *et al.* 2013). Each item of PANSS is scored on a seven-point Likert scale, with a score of 1 denoting that the item being measured is 'absent', a score of 2 denoting that it is 'minimal' (indicating 'questionable or subtle or suspect pathology') and a score of 3 denoting 'mild' (indicating 'a symptom whose presence is clearly established but not pronounced'). Higher scores on each of these items indicate greater severity. A score of 3 was used as the cut-off as it denotes 'mild' severity, indicating 'a symptom whose presence is clearly established but not pronounced', and is the threshold used in the clinical setting to indicate clear, unambiguous presence of a psychotic symptom (Kay *et al.* 1987). Psychotic symptoms scored in these participants were otherwise comparable to that observed in a clinical situation except for the transient nature of psychotic symptoms observed under the experimental THC challenge condition. For our exploratory analyses, participants were classified into those who experienced transient anxiety (TA) and those who did not (NA) under the influence of THC on the basis of a greater (TA) or lesser (NA) than four-point change in their STAI (when baseline STAI score was deducted from their peak post-THC STAI score) in response to THC administration. This cut-off was determined using the Reliable Change Index (Jacobson & Truax, 1991).

Image acquisition

fMRI scans were acquired using a 1.5 tesla scanner (see supplementary methods). During fMRI acquisition, subjects completed a verbal paired associate learning task (Bhattacharyya *et al.* 2009), which comprised encoding, recall and baseline conditions. For the encoding condition, subjects were required to indicate whether visually presented word pairs were related in terms of their meaning, while during a subsequent recall condition, they were presented with one word from each pair presented before and were required to recall the missing word that had been previously associated with the word. During the baseline condition, subjects were presented with word pairs with identical or different fonts and they were asked to indicate if the fonts were identical. For each of the conditions, eight stimuli pairs were presented sequentially across four blocks. Recall score was used as a measure of task performance during the memory task. Analysis of performance data suggested a ceiling effect by the third block (online Supplementary Fig. S1) and hence only data from the first three blocks were analysed.

Data analysis

Psychological ratings and memory task performance were analysed using SPSS version 22. Socio-demographic characteristics (such as age, NART score and number of years in education) and task performance (recall score) of the groups (TP *v.* NP and TA *v.* NA) were compared using two-sample *t* tests, while symptom data at 2 h after THC and placebo administration were compared using Mann–Whitney U tests as they did not fit normal distribution.

Imaging data were pre-processed and analysed (following previously reported approaches) using XBAMv4.1 (http://www.brainmap.co.uk), a non-parametric image analysis programme that minimizes assumptions about the distribution of the data, which is important in fMRI where the data may not follow a Gaussian distribution(Thirion *et al.* 2007) (see online Supplementary Methods).

For each drug condition, we contrasted each of the active (encoding or recall) conditions of the verbal memory task against the baseline (fonts) condition at the individual subject level to generate contrast of interest map ('encoding minus baseline' and for 'recall minus baseline' conditions) for each subject, which were used for subsequent group-level analyses (TP *v.* NP and TA *v.* NA).

To investigate our primary hypothesis that 'TP PLB' group would show greater hippocampal activation compared with the 'NP PLB' group, analysis of variance (ANOVA) compared the 'TP PLB' group and the 'NP PLB' group during the placebo condition in order to assess differences in functional activation during the contrast of interest (for 'encoding minus baseline' and for 'recall minus baseline' conditions, henceforth referred to as 'encoding' and 'recall', respectively, unless otherwise specified) in the absence of THC. To test the robustness of these group differences in activation and whether they were driven by outliers, we carried out a 'leave one subject out' (LOSO) analysis, which involved repeating the ANOVA with a different subject from the TP group being left out on each repeat. A total of 14 repeat ANOVAs were carried out, once with each of the 14 'TP PLB' subjects being left out. We then carried out exploratory analyses to examine whether these brain activation differences during the encoding and recall conditions were specific to the subgroups classified according to sensitivity to the psychotomimetic effects of THC ('TP PLB' *v.* 'NP PLB') or were similar to that between subgroups classified based on sensitivity to anxiogenic effects of THC ('TA PLB' *v.* 'NA PLB'). One-way ANOVA compared task-related brain activation differences (during encoding and recall conditions) between the 'TA PLB' and 'NA PLB' groups under the placebo condition to examine whether similar group differences exist between the 'TA PLB' and 'NA PLB' groups as between the 'TP PLB' and 'NP PLB' groups. To test our hypothesis that THC administration would modulate brain activation differently in the TP and NP groups, further comparisons (using two-way ANOVA) were then made between the drug given, TP and NP groups and the interaction of effects between them. Statistical values from differentially activated brain clusters (mean of all voxels in the cluster) were used to identify correlation with behavioural data to test our hypothesis that difference in brain activation under the placebo condition between the TP and NP groups would be directly associated with the magnitude of THC-induced psychotomimetic effects in the same individuals. A similar approach was employed to compare the 'TA PLB' and 'NA PLB' groups.

Results

Symptomatic and behavioural differences between TP and NP

Of the 36 subjects who participated in the study, 14 satisfied our pre-defined criteria on the basis of PANSS ratings following THC administration to be classified to the TP group, whilst the remaining 22 subjects formed the NP group. These two groups were not significantly different in terms of their socio-demographic characteristics and estimated pre-morbid IQ ($p > 0.5$) (Table 1) or in terms of symptoms experienced under the placebo condition (Mann–Whitney *U* tests $p > 0.4$; Fig. 1; online eTable 2).

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Table 1. Socio-demographic variables

	Transiently psychotic (*n* = 14)	Non-psychotic (*n* = 22)	*p* Value
Mean age, years (S.D.)	25.86 (5.14)	26.05 (5.96)	0.92
Mean NART Score (S.D.)	97.07 (8.32)	98.24 (5.37)	0.65
Mean years in education (S.D.)	16.58 (4.06)	17.41 (4.40)	0.59
	Transiently anxious (*n* = 18)	Non-anxious (*n* = 18)	*p* Value
Mean age, years (S.D.)	26.56 (6.00)	25.39 (5.24)	0.53
Mean NART score (S.D.)	100 (4.38)	95.61 (7.70)	0.04
Mean years in education (S.D.)	16.94 (3.21)	17.28 (5.07)	0.81

S.D. is standard deviation reported within brackets.

However, 2 h after the administration of THC, the 'TP THC' group scored significantly higher on both the STAI ($p = 0.008$) and AIS ($p = 0.001$) ratings (Fig. 1; online Supplementary Table S2). As expected, following THC administration, the 'TP THC' group showed marked increases in all PANSS subscale scores (Fig. 1) which were significantly higher than the NP group for all of the PANSS subscales (Mann–Whitney *U* tests; all $p < 0.001$; online Supplementary Table S2). Both the TP ('TP THC' and 'TP PLB') and NP ('NP THC' and 'NP PLB') groups showed similar total recall scores under both THC (*t* tests; $p = 0.85$) and placebo conditions ($p = 0.22$) (online Supplementary Table S2).

Of the total sample, 18 participants were assigned to the TA group and 18 were assigned to the NA group based on their STAI ratings following THC administration. The two groups were well matched on age and years of education; however, there was a significant difference between NART-IQ scores between the TA and NA groups ($p = 0.04$; Table 1). The 'TA THC' group had higher STAI scores compared with the 'NA THC' group following THC administration ($p = 0.016$; online Supplementary Table S2). However, they were not significantly different ($p = 0.18$) in terms of the severity of transient psychotic symptoms (PANSS-Positive subscale) induced by THC. Both

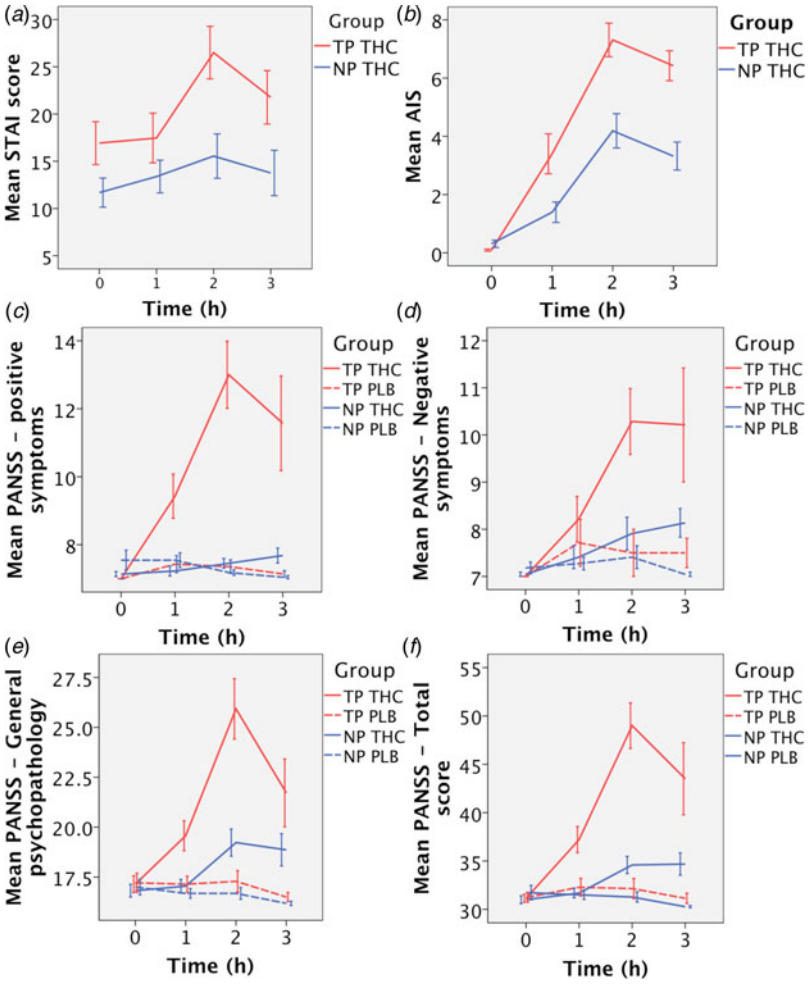

Fig. 1. Changes in anxiety, intoxication and psychotic symptoms under the THC condition. Line graphs show anxiety (*a*: State-Trait Anxiety Inventory-State; STAI) and intoxication (*b*: analogue intoxication scale; AIS) ratings for both the transiently psychotic (TP THC) and non-psychotic (NP THC) group recorded before (0 h) and 1, 2 and 3 h after drug administration. Line graphs show ratings on positive (*c*), negative (*d*), general psychopathology (*e*) subscales and total score (*f*) of the Positive and Negative Syndrome Scale (PANSS) for both the transiently psychotic group (TP) and non-psychotic group (NP) following the administration of THC (TP THC and NP THC) and placebo (TP PLB and NP PLB) recorded before (0 h) and 1, 2 and 3 h after drug administration. Error bars represent standard error of the mean.

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groups also showed similar total recall scores under both placebo and THC (online Supplementary Table S2).

Of the 14 TP participants, eight were also in the TA group based on their anxiety ratings and six were in the NA group. Of the 22 NP participants, 10 were in the TA group and 12 in the NA group. There was a positive correlation (0.41, $p = 0.01$) between transient psychotic symptoms (PANSS-Positive subscale) and anxiety (STAI) measured 2 h after administration of THC.

Brain regions engaged by the verbal memory task in all individuals

As expected, during both the encoding and recall conditions in all study participants, the verbal memory task was associated with engagement of brain regions previously implicated in memory processing, particularly the prefrontal and medial temporal cortices (encoding: online Supplementary Table S3A, Fig. S2A; and recall: online Supplementary Table S3B, Fig. S2B).

Differences in activation between the 'TP PLB' and 'NP PLB' groups under placebo

Investigation of our hypothesis that 'TP PLB' group would show greater hippocampal activation compared with the 'NP PLB' group showed that during the encoding condition, there was greater engagement of the left hippocampus, left anterior cingulate (ACC) and right superior temporal gyrus (STG) ($p < 0.001$, corrected for <1 false-positive cluster) in the 'TP PLB' group than the 'NP PLB' group, whereas the converse was true in the cerebellum bilaterally (Fig. 2; online Supplementary Table S4). Left hippocampal engagement remained significantly different between the 'TP PLB' and 'NP PLB' groups across all repeats of the LOSO analysis (which involved repeating the ANOVA with a different subject from the 'TP PLB' group being left out on each repeat), whereas the clusters of activation in the STG and ACC did not consistently survive this analysis. As there was a direct correlation between the transient psychotic symptoms and anxiety induced following THC administration, *post hoc*, we compared the 'TP PLB' and 'NP PLB' groups during the encoding condition under placebo after controlling for the severity of anxiety symptoms induced under THC. This did not change the pattern and direction of results (data not shown, but available from the authors on request), particularly the difference in left hippocampal engagement between the 'TP PLB' and 'NP PLB' groups.

In order to examine whether the group difference in activation between the 'TP PLB' and 'NP PLB' groups truly represented a marker of sensitivity to the psychotomimetic effects of THC, we then tested whether activation in these regions under placebo condition was directly related to the severity of transient psychotic symptoms induced by THC in these individuals. Engagement of the left hippocampus under placebo condition showed a non-linear correlation with the increase in the severity of psychotic symptoms following administration of THC (Spearman's $\rho = 0.44$, $p = 0.008$; Fig. 2*d*).

During the recall condition, significant between-group differences ('TP PLB' *v.* 'NP PLB") in activation were observed in the left medial frontal, right middle temporal gyrus and anterior lobe of cerebellum, where the 'TP PLB' group showed greater engagement relative to the 'NP PLB' group, whereas the converse applied in the left inferior parietal lobule, the precentral gyrus bilaterally, the precuneus and cingulate gyrus on the right side and the posterior lobe of the cerebellum (online Supplementary Fig. S3 and Table S4). Group ('TP PLB' *v.* 'NP PLB') differences in activation in these regions did not always survive the LOSO analysis and were not investigated further.

Specificity of brain activation differences between the 'TP PLB' and 'NP PLB' groups under placebo

Exploratory one-way ANOVA revealed significant differences in task-related activation between the 'TA PLB' and 'NA PLB' groups under the placebo condition during both the encoding (online Supplementary Table S5, Fig. S4) and the recall (online Supplementary Table S5, Fig. S5) conditions. However, these regions did not overlap with those that were differentially activated on contrasting the 'TP PLB' and 'NP PLB' groups.

Differences in activation between the TP and NP groups under THC

Investigation of our hypothesis that THC administration would modulate brain activation differently in the TP and NP groups, reflecting the different symptomatic effects with two-way ANOVA [group (TP *v.* NP) by drug (THC *v.* placebo)] revealed significant differences in the effect of THC on activation in the two groups in a number of areas during the encoding but not the recall condition (Fig. 3; online Supplementary Table S4). Under placebo during the encoding condition, there was greater engagement of the right middle frontal gyrus (MFG) extending to the precentral gyrus and in the left cingulate gyrus and cerebellum in the 'TP PLB' group relative to the 'NP PLB' group. However, under the THC condition there was a reversal of engagement of these regions: THC attenuated their activation in the 'TP THC' group but augmented it in the 'NP THC' group, relative to placebo. The THC-induced change in activation of the right MFG inversely correlated with increase in the severity of psychotic symptoms following THC (Spearman's $\rho = -0.6$, $p \leqslant 0.001$; Fig. 3*c*). There was no significant group (TP *v.* NP) by drug (THC *v.* placebo) interaction in the left hippocampus where there was a difference between the 'TP PLB' and 'NP PLB' groups under placebo condition, nor was a similar difference observed between the 'TP THC' and 'NP THC' groups under THC alone.

Discussion

Here we investigated whether differences in hippocampal activation measured using BOLD fMRI under placebo conditions may distinguish between healthy males who are sensitive to the psychotomimetic effects of THC from those who are not. The results suggest that altered activation in the left hippocampus area implicated in both normal memory processing and the neuropathology of psychosis, differentiated those who experience transient psychotic symptoms following a single dose of THC from those who do not.

These differences were not simply a result of differential levels of task performance in these two groups, nor were they related to group differences in socio-demographic characteristics or psychological ratings at the time the neuroimaging data were acquired. As predicted, increased encoding-related engagement of the left hippocampus, a region critical for encoding (Eichenbaum *et al.* 2007), differentiated the THC-sensitive group from those not sensitive to its psychotomimetic effects. Furthermore, left hippocampal engagement which reliably differentiated healthy

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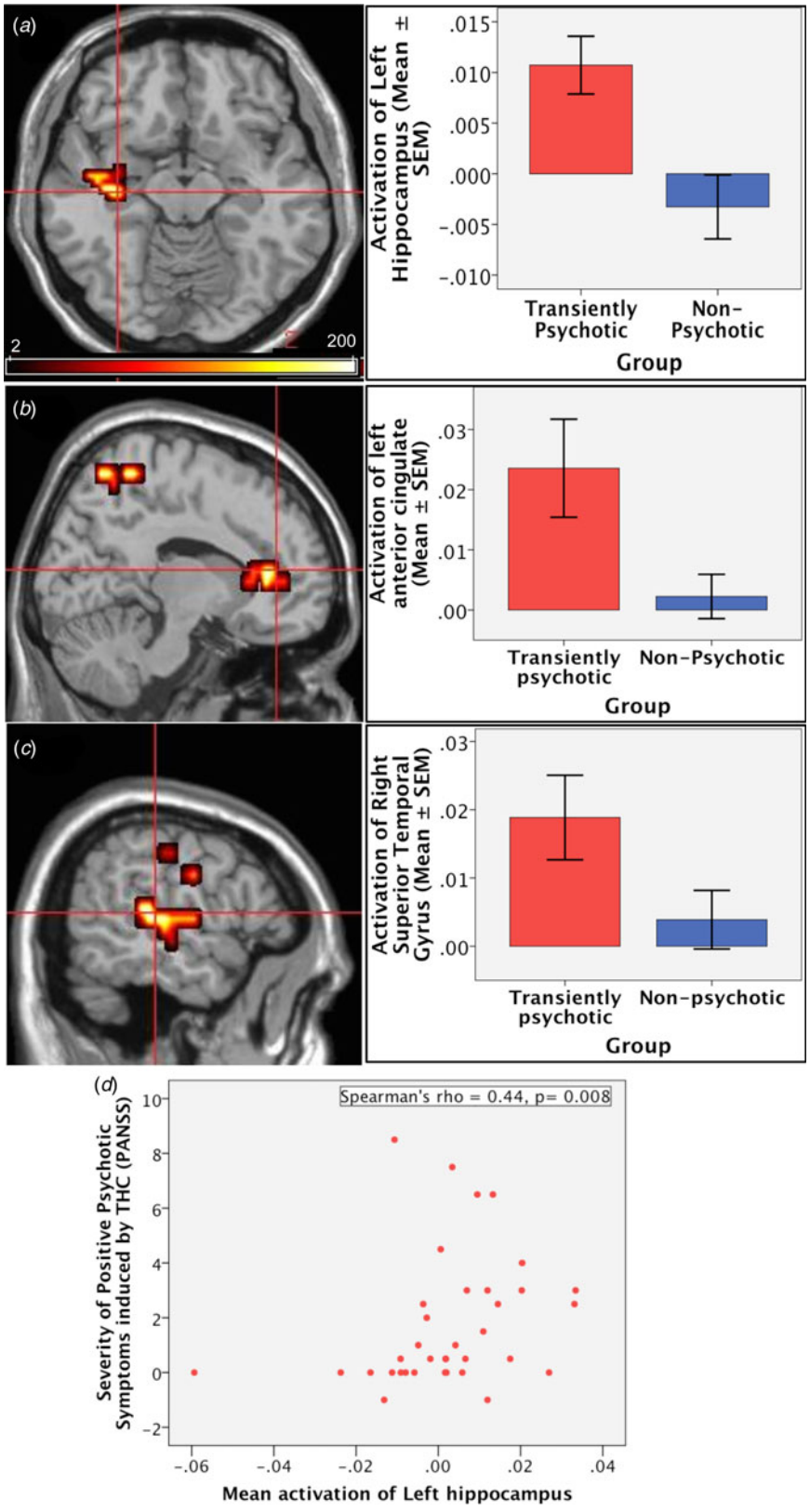

Fig. 2. Brain activation differences between those sensitive to the psychotomimetic effects of THC (TP PLB) *v.* those who were not (NP PLB) under placebo during the encoding condition of the verbal learning task. Brain sections on the left column show greater engagement of the left hippocampus (*a*), left anterior cingulate (*b*) and right superior temporal gyrus (*c*) in the transiently psychotic (TP PLB) compared with the non-psychotic (NP PLB) group during encoding under the placebo condition. Bar charts on the right column display the mean brain activation (error bars represent standard error of mean; S.E.M.) values (arbitrary units) from the corresponding brain regions. All results are significant at $p < 0.008$ (cluster p values corrected to yield <1 false-positive cluster). Left side of the brain is shown on the left side of the brain images. Scatter plot (*d*) displays the non-linear correlation between engagement of the left hippocampus under placebo condition with the increase in severity of psychotic symptoms following administration of THC (Spearman's $\rho = 0.44$, $p = 0.008$).

individuals on the basis of their sensitivity to acute psychotomimetic effects of THC, was directly correlated with the severity of psychotic symptoms induced under the influence of THC, such that the greater the engagement of the left hippocampus under the placebo condition, greater was the severity of psychotic symptoms induced by THC. This was consistent with our hypothesis that difference in brain activation under the placebo condition between the TP and NP groups would be directly associated with the magnitude of THC-induced psychotomimetic effects in the same individuals. Difference in hippocampal engagement

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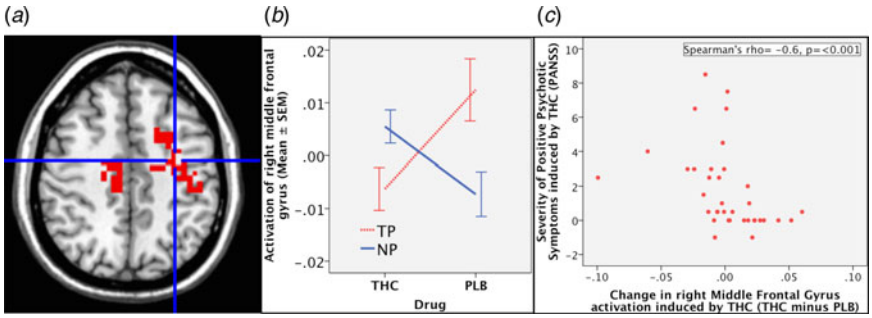

Fig. 3. Brain activation differences between those sensitive to the psychotomimetic effects of THC (TP) *v.* those who were not (NP) under THC relative to placebo treatment during the encoding condition of the verbal learning task. Brain section (*a*) displays a cluster in the right middle frontal gyrus (MFG) extending to the precentral gyrus (cross-hair) and a cluster in the left cingulate, where there was greater engagement (shown in bar chart *b*; mean brain activation and error bars represent standard error of mean, S.E.M.; all values in arbitrary units) under placebo treatment in the TP group relative to the NP group, which was reversed under THC treatment condition. Left side of the brain is shown on the left side of the brain image. THC-induced change in activation of the right MFG inversely correlated (scatter plot *c*) with increase in severity of psychotic symptoms under THC (Spearman's $\rho = -0.6$, $p \leqslant 0.001$).

distinguished individuals sensitive to the psychotomimetic effects of THC but not those who experienced anxiety under THC as revealed in exploratory analyses, suggesting the relationship was specific to psychotic symptoms. This difference in hippocampal engagement persisted even after controlling for the severity of THC-induced anxiety suggesting that difference in hippocampal activation under placebo condition between the 'TP PLB' and 'NP PLB' individuals was not a marker of differential sensitivity to THC-induced anxiety in the same individuals. Collectively, these findings suggest that increased left hippocampal engagement during word encoding may be a marker of sensitivity to the acute psychotomimetic effects of THC. This is consistent with evidence of increased resting hippocampal regional cerebral blood flow (Allen *et al.* 2016) in those at high clinical risk of psychosis and reduced hippocampal volume in those with established schizophrenia (Nelson *et al.* 1998). However, it is worth noting that it is regular rather than acute cannabis use that has been linked to schizophrenia. Hence, while altered left hippocampal engagement may be a marker of sensitivity to the acute psychotomimetic effects of THC, it may not necessarily be a marker of sensitivity to the development of schizophrenia following regular cannabis use.

By definition, the TP and NP groups had different responses to THC in relation to their levels of acute psychotic symptoms. Consistent with our hypothesis that THC administration would modulate brain activation differently in the TP and NP groups, our second major finding was that this difference in psychotic symptom generation was associated with a difference in the neurophysiological effects of THC in the two groups. There was a significant interaction between drug and group in the MFG, a region involved in the organization of memory (Simons & Spiers, 2003). Attenuation of lateral prefrontal activity by THC in our study correlated with the increase in psychotic symptoms induced by it, and is consistent with a similar attenuation of lateral prefrontal activity (Bhattacharyya *et al.* 2015*a*) by THC that correlated with the severity of psychotic symptoms (Bhattacharyya *et al.* 2015*a*) induced by it as well as genetic moderation (Bhattacharyya *et al.* 2014) of the effects of THC in this region in the context of a cognitive activation task that engaged inhibitory control processes. Altered brain activity in this region has also been shown in the context of inhibitory and related motor control tasks in cannabis users both under acute THC challenge condition (Weinstein *et al.* 2008) and in its absence (Eldreth *et al.* 2004; Tapert *et al.* 2007). The lateral prefrontal cortex is rich in CB1 receptors (Elphick & Egertova, 2001), the main target of THC in the brain (Pertwee, 2008), and the results presented here suggest that the effects of THC in this region may be involved in the generation of paranoia under its influence consistent with dorsolateral prefrontal hypoactivity reported in schizophrenia (Callicott *et al.* 2000) and role of altered lateral prefrontal activity in the pathophysiology of psychotic symptoms in schizophrenia (Shergill *et al.* 2000).

We have previously reported that the normal pattern of medial temporal engagement while learning new information is altered by an acute THC challenge (Bhattacharyya *et al.* 2009). The present study extends this by establishing that altered hippocampal engagement during a memory task distinguishes those healthy individuals who are particularly sensitive to the acute psychotomimetic effects of THC from those who are not.

Limitations

The results presented here should be considered preliminary in light of certain limitations. An important caveat relates to the generalizability of these results under laboratory conditions to the small proportion of real-world cannabis users who may be sensitive to the psychotomimetic effects of THC, which may be manifest on a continuum from mild transient paranoia to frank schizophreniform disorder. It is worth noting that psychotic-like symptoms experienced by participants in this study were transient and self-limited unlike those observed in established psychosis, but not dissimilar to the transient paranoia experienced by large number of cannabis users. We ensured that the psychotic symptoms experienced by participants classified as part of the transiently psychotic group were qualitatively similar to overt psychotic symptoms such as delusions and hallucinations and not merely a result of behavioural disorganization, by setting a cut-off threshold identical to that employed in clinical practice. It is also worth noting the present study does not account for other factors such as genetic (van Winkel *et al.* 2011; Di Forti *et al.* 2012; Bhattacharyya *et al.* 2012*a*, 2014) and personality and familial factors (McGuire *et al.* 1995; Henquet *et al.* 2005; Stirling *et al.* 2008) as well as the composition (Bhattacharyya *et al.* 2010) and dose (Schoeler *et al.* 2016*c*) of cannabis that may also underlie differential sensitivity to the effects of cannabis.

It may also be argued that the articulation of verbal responses during the task may have resulted in head movement, which would have affected brain activation that in turn may have influenced our results. An effect of articulation seems unlikely because the findings in our study were obtained from comparisons of repetitions of the same condition between groups or between the effects of drugs on the same conditions in the two groups.

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As the verbal responses in these comparisons were identical, even if articulation had affected the fMRI signal, it would have had to have a systematically different effect between the two groups (TP *v.* NP) or in the presence of one drug *v.* another. This seems unlikely, as there was no change in the demands on articulation between the two groups or between the drug conditions, and there was no significant difference in the performance of the task between the groups under the two drug conditions. We thus think that it is highly unlikely that head movement due to verbal responses during the task significantly affected the results.

Similarly, one may suggest that expectation or memory of the psychotomimetic effects of THC may partly account for the brain activation differences between the TP and NP groups. However, this is also unlikely to fully account for these findings, as such an effect on brain activation should have been similarly evident on comparison of the TA and NA groups, which it was not. Furthermore, because of the very nature of this study, individuals with marked psychosis-like effects during previous cannabis use may have been less likely to volunteer for such a study, suggesting that any effect of expectation or memory of psychotomimetic effects of THC is unlikely to have been substantial. It is also worth noting that participants in this study had limited previous exposure to cannabis. Hence, even if such an effect had been present, it is likely that this would have been cancelled out on comparison of two groups with minimal previous exposure to cannabis (TP *v.* NP).

It is also important to note that this study cannot establish whether association between hippocampal activation and sensitivity to the psychotomimetic effects of THC was specific to the use of a verbal paired associate learning task as opposed to cognitive paradigms that engage other cognitive processes affected by THC, as we did not investigate this. Future systematic investigation in this area may be warranted. Finally, the relatively modest sample size of the present cohort should also be noted, highlighting the need for independent replication in larger samples.

Collectively, our results suggest altered hippocampal activation may underlie sensitivity to the acute psychotomimetic effects of THC under experimental conditions in occasional cannabis users. While one may speculate that altered hippocampal activation may also predict sensitivity to the onset of psychotic disorders or a relapse of psychosis following regular cannabis use, this was not tested here and will require further investigation in prospective studies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718000387

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