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Impaired learning from errors in cannabis users: Dorsal anterior cingulate cortex and hippocampus hypoactivity

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ABSTRACT

Background: The chronic use of cannabis has been associated with error processing dysfunction, in particular, hypoactivity in the dorsal anterior cingulate cortex (dACC) during the processing of cognitive errors. Given the role of such activity in influencing post-error adaptive behaviour, we hypothesised that chronic cannabis users would have significantly poorer learning from errors.
Methods: Fifteen chronic cannabis users (four females, mean age = 22.40 years, *SD* = 4.29) and 15 control participants (two females, mean age = 23.27 years, *SD* = 3.67) were administered a paired associate learning task that enabled participants to learn from their errors, during fMRI data collection.
Results: Compared with controls, chronic cannabis users showed (i) a lower recall error-correction rate and (ii) hypoactivity in the dACC and left hippocampus during the processing of error-related feedback and re-encoding of the correct response. The difference in error-related dACC activation between cannabis users and healthy controls varied as a function of error type, with the control group showing a significantly greater difference between corrected and repeated errors than the cannabis group.
Conclusions: The present results suggest that chronic cannabis users have poorer learning from errors, with the failure to adapt performance associated with hypoactivity in error-related dACC and hippocampal regions. The findings highlight a consequence of performance monitoring dysfunction in drug abuse and the potential consequence this cognitive impairment has for the symptom of failing to learn from negative feedback seen in cannabis and other forms of dependence.

1. Introduction

The chronic use of cannabis has been associated with a range of cognitive impairments, including impairments in learning, memory, and executive functions (Crean et al., 2011; Ranganathan and D'Souza, 2006), with a dose–response relationship between chronicity of cannabis consumption and deterioration in these cognitive domains (Messinis et al., 2006). While there remains equivocation regarding the specific nature of the executive function impairments in the cannabis-using population (Grant et al., 2002) – likely due to diverse methodologies and measures employed (Verdejo-García et al., 2004) – there is more consistent evidence of impairments in learning (see Solowij and Battisti, 2008 for a review). Of particular interest to the current study is dysfunction in error learning in chronic cannabis users (CCU), because difficulty in adjusting behaviour in the face of negative consequences is a core clinical symptom of cannabis dependence and other drug dependencies (Kalivas and Volkow, 2005).

Error processing refers to monitoring performance, detecting errors, and modifying behaviour adaptively in the absence of overt reinforcement (Holroyd and Coles, 2002). Error processing dysfunction has been demonstrated in several psychiatric conditions, including schizophrenia (Becerril et al., 2011; Mathalon et al., 2009; Morris et al., 2008), depression (Chiu and Deldin, 2007; Steele et al., 2004; Tucker et al., 2003) and a range of drug dependencies (Connolly et al., 2012; Easdon et al., 2005; Forman et al., 2004; Li et al., 2010). In all these conditions, the dysfunction is characterised by hypoactivity in the error-related network, most consistently in the dorsal anterior cingulate gyrus (dACC). While relatively few studies have investigated error processing in chronic cannabis users (see Spronk et al., 2011 for a study of the acute effects on non-users), the typical pattern of hypoactivity in the dACC (along with other key error-related regions such as the insula) has recently been demonstrated (Hester et al., 2009). Thus, there is evidence to suggest that performance monitoring is impaired

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in chronic cannabis users, although the consequence for adaptive post-error behaviour remains unclear.

The dorsal anterior cingulate cortex (dACC; Fitzgerald et al., 2010; Ridderinkhof, 2004; Ullsperger and von Cramon, 2003) and mesial temporal memory structures (Squire et al., 2004) have been consistently implicated in reinforcement learning. The magnitude of dACC activation has been associated with adaptive changes following an error. Greater dACC activation has been associated with individuals slowing their response following the error (Debener et al., 2005; Garavan et al., 2002), with post-error slowing thought to reflect cautiousness and to be linked with future behavioural changes ("learning"). Research in drug-dependent populations has consistently linked error-related hypoactivity in the dACC with a lack of post-error slowing (Forman et al., 2004; Franken et al., 2007; Hester et al., 2007), though the relationship between slowing and adaptive behaviour is often difficult to demonstrate with some cognitive paradigms. Similarly, the dACC has also been implicated in other adaptive behaviours (Agam et al., 2011), with greater activation in the dACC associated with making fewer commission errors (Ghahremani et al., 2010; Polli et al., 2008). Chronic cannabis using samples have also shown hypoactive dACC activity during dysfunctional control performance (Gruber and Yurgelun-Todd, 2005; Wesley et al., 2011) that was associated with poorer overall task performance. Recent research has demonstrated that error-related dACC activity predicts learning from errors, despite a substantial delay between the error and the opportunity to correct the error (Hester et al., 2008, 2010). In particular, the relationship between error-related activity in the dorsal ACC and re-encoding related activity in the hippocampus was particularly critical to successful learning from errors.

Error processing dysfunction in drug abusing populations has been found to increase the likelihood of drug-seeking behaviour and interfere with a user's capacity to assimilate and participate in rehabilitation programs that have an educative and cognitive emphasis (Sofuoglu et al., 2010; Verdejo-García et al., 2004). The purpose of the current study was to examine error processing in chronic cannabis users by utilising a combined neuroimaging and behavioural approach. Given the previous findings of error-related hypoactivity in cannabis users (Hester et al., 2009), we sought to examine the relationship between error-related dACC activity and learning from errors in cannabis users and controls, using a paired associate learning task (2008).

We hypothesised that chronic cannabis users would have poorer recall on the paired associate learning task, with significantly lower error correction rate when taking into account the poorer initial performance. It was also hypothesised that chronic cannabis users would have hypoactivity in the dACC and hippocampus during error processing in comparison to controls, and that this hypoactivity would be associated with poorer error correction rate.

2. Methods

2.1. Sample and participant selection

Fifteen chronic cannabis users (four females, mean age = 22.40 years, *SD* = 4.29, range = 18–33) and 15 control participants (two females, mean age = 23.27 years, *SD* = 3.67, range = 19–33) were recruited via leaflet advertising at Trinity College Dublin, Dublin, Ireland. Written informed consent was obtained from all participants following complete description of the study. Groups were matched for educational attainment, $t(28) = 1.23$, $p = .229$, and estimated pre-morbid IQ, via the National Adult Reading Test (NART; Nelson, 1982), $t(28) = -0.60$, $p = .555$ (see Table 1). A semi-structured interview was used to screen participants for past or present history of psychiatric or neurological illness. Participants were interviewed using a self-report form that screened for a history of diagnosed psychiatric or neurological illness, including prompts for the 20 most commonly diagnosed conditions in the age-group sampled (college students). Participants were also asked to report any current undiagnosed symptoms that they were experiencing, which were followed up with verbal questions to clarify the type, intensity and duration of symptoms. Information pertaining to any form of treatment (counselling, psychological, psychiatric), past or present, was carefully detailed, with any potential participant describing any major life-time psychiatric event or brain injury (e.g., head trauma resulting in a loss of consciousness, seizure or stroke) considered ineligible for the study. Participants were also considered ineligible if they reported any familial psychiatric history (i.e., sibling, parent or grandparent).

Table 1
Means (standard error) for control ($n = 15$) and cannabis ($n = 15$) groups on demographic and drug use history.

	Controls *M* (*SE*)	Cannabis users *M* (*SE*)
Age	23.27 (0.95)	22.40 (1.11)
Years of education	18.27 (0.76)	17.13 (0.52)
Verbal intelligence score (NART)	108.51 (0.38)	109.02 (0.77)
Beck Depression Inventory-II score*	2.13 (0.53)	5.73 (1.35)
Females/males	4/11	2/13
Number of nicotine smokers	40%	47%
Years of alcohol use	4.17 (0.73)	2.84 (1.15)
Alcohol use in last month (no. of days)	5.47 (1.25)	7.77 (1.68)
Alcohol use age onset (years)	14.39 (1.68)	15.60 (0.46)
Cannabis use (years)	0.00 (0.00)	6.43 (1.07)
Lifetime joints (number)	0.33 (0.21)	7341.40 (2340.80)
Days of use in last month (number)	0.00 (0.00)	20.80 (26.66)
Joints in last month (number)	0.00 (0.00)	72.47 (12.60)
Cannabis use age onset (years)		15.97 (0.42)
Cannabis abstinence (hours)		101.67 (37.45)
Cannabis withdrawal score (out of 32)		12.60 (2.22)
Cannabis craving scores (*each item out of 21*)		
Compulsivity		6.20 (0.76)
Emotionality		7.67 (1.26)
Expectancy		11.13 (1.10)
Purposefulness		12.47 (1.41)

Note: NART = National Adult Reading Test.
* $p < .05$ statistically significant difference between groups.

In order to screen for past or current abuse of other substances, all participants completed the inventories of drug use subsection of the Addiction Severity Index Lite (Clinical Factors version) questionnaire (McLellan et al., 1999). Prospective participants from either group were considered ineligible if they reported concurrent or past dependence on other drugs (including tobacco and alcohol). Information concerning alcohol and cannabis use in each participant was indexed in number of years (lifetime) and occasions of recent use (last 30 days) and is presented in Table 1.

In order to be eligible for participation in this study, participants in the cannabis group were required to have regularly consumed cannabis (5–7 days/week) for the previous 2 years and to have smoked a minimum of 500 joints in their lifetime. All cannabis users provided a positive urine sample for Δ^9-tetrahydrocannabinol (Δ^9THC) before scanning, with an additional screening for other confounding drug use (Cozart RapiScan, Abingdon, UK) taking place. Control participants were also urine tested for Δ^9THC and other drugs. Prospective participants with a past or present diagnosis (or self-reported symptoms consistent with a current diagnosis) of psychiatric or neurological illness were excluded. Participants providing positive tests for drugs other than cannabis (cannabis group only) were excluded, and all participants provided a breath test 0% blood alcohol concentration reading before the beginning of the cognitive testing.

2.2. Experimental protocols

A paired associate learning task (Hester et al., 2008), consisting of an array of location–number associations that were to be learned by participants, was administered (Fig. 1). All aspects of stimulus delivery and response recording were controlled by E-Prime software (version 1.1; Psychology Software Tools), running on a laptop PC (Celeron 2-GHz, 128 Mb Nvidia video card) that was interfaced with the magnetic resonance (MR) scanner during fMRI acquisition. The task began with an encoding phase in which eight locations designated as light grey squares were presented simultaneously on a dark grey background. The locations of the squares on the background were selected in a quasi-random fashion from an 8×8 matrix, with two locations randomly chosen from each of the four quadrants on the display.

At the commencement of the encoding phase, each location in turn had superimposed upon it a two-digit number. The number remained visible for 2 s, and was

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