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The effects of sex and residual cannabis use on emotion processing:

An event-related potential study

Lucy J. Troup, Jeremy A. Andrzejewski, and Robert D. Torrence

Colorado State University

Author Note

Lucy J. Troup, Department of Psychology, Colorado State University; Jeremy A. Andrzejewski, Department of Psychology, Colorado State University; Robert D. Torrence, Department of Psychology, Colorado State University.

Lucy J. Troup is now at the Strategic Hub Psychology, Social Work, Health Behaviors and Addictions, University of the West of Scotland; Jeremy A. Andrzejewski is now at the Department of Psychological Science, Northern Michigan University; Robert D. Torrence is now at the Department of Pharmacy Practice, Wayne State University.

Correspondence concerning this article should be addressed to Lucy J. Troup, Strategic Hub Psychology, Social Work, Health Behaviors, University of the West of Scotland, Paisley, Scotland. Email: Lucy.Troup@uws.ac.uk
Public Significance Statement

This study found significant differences in the processing of emotion in relation to cannabis use patterns between males and females. This suggests that when considering the implications of the effects of cannabis use it is important to address sex differences in particular in relation to emotion processing and emotion processing disorders such as anxiety, depression and PTSD.

Abstract

Cannabis use has been shown to affect processing of emotional facial expressions as measured by the P1 and P3 event-related potential (ERP) components. These components have been shown to be related to emotion processing in particular attention to emotion. Previous research also indicates that there are sex differences in how cannabis effects males and females as well as how they process emotion. This study examined the relationship between the effects of residual cannabis use and sex differences in 144 participants (F = 80) in a facial expression emotion processing task. Both the P1 and P3 ERP components were compared in male and female participants in non-cannabis user, casual cannabis user and heavy cannabis user groupings. The task involved implicitly, explicitly and empathically identifying emotional expressions (angry, happy neutral and fearful) in male and females faces. There were differences between males and females in both the P1 and P3 ERP in relation to cannabis use. Males had a larger P1 than females with cannabis use and a smaller P3. Differences in the P1 were observed in both positive and negative emotion and between tasks in relation to cannabis use patterns. Differences in the P3 were seen in heavy male users for empathy happy and casual male users implicit angry when compared to females. These differences highlight the important of considering sex differences in regard to the effects of cannabis, in particular in emotion processing.

Keywords: Cannabis, Emotion processing, Sex differences, Event related potentials, ERPs
Disclosures and Acknowledgements

Lucy J. Troup PhD
Senior Scientist, instrumental in the design and implementation of the project including being senior author and preparing the manuscript for publication.

Robert D. Torrence PhD
Instrumental in data collection and analysis as well as preparing the manuscript for publication.

Jeremy A. Andrzejewski BSc
Instrumental in data collection and analysis as well as preparing the manuscript for publication.

All Authors have read and approved the manuscript for publication.
The effects of sex and residual cannabis use on emotion processing:

An event-related potential study

The relationship between cannabis use and sex differences is complex. There is a well-defined body of literature that has investigated the relationship between males and females and their use patterns and their motivations for use (e.g. Kandel & Chen, 2000; Tu, Ratner & Johnson, 2008; Kerridge, Pickering, Chou, Saha, & Hasin, 2018) as well as the clinical effects (e.g. Kerridge et al., 2018; Rubino & Pralaro, 2015; Khan et al., 2013). Differences in the effects of cannabis on neurological effects based purely on biological sex is less well defined.

**Sex differences in cannabis use behaviors and brain structure and function**

Changes in the legal status of cannabis in some states has led to an increased interest in the effects of cannabis on brain function and behavior. Neurobiological studies have shown that there are sex related differences in brain structure between male and female cannabis users compared to controls (e.g. Craft, 2005; Medina et al., 2007; Nagel, Hanson, Yang, & Tapert, 2009; Fattore & Fratta, 2010; McQueeny et al., 2011). In particular differences in the volume of the pre-frontal cortex (PFC), with female cannabis users showing greater volume and male cannabis users’ smaller volume than same sex controls (Medina et al., 2009). Also reported are differences in the amygdala, with female cannabis users showing an increase in amygdala volume compared to males and non-using controls, which was associated with internalizing of symptoms of anxiety and depression (McQueeny et al., 2011). As gender differences in cannabis use disorder (CUD) and psychopathy is relatively well documented, with males showing a significant comorbidity between CUD a second psychiatric diagnosis for antisocial personality disorder whereas females more likely to have a secondary diagnosis of mood disorders (Khan et al, 2013). Studies focusing on functional changes under the influence of cannabis suggest there
are significant differences in brain function between cannabis users and non users. Recent reviews of the functional differences reported in cannabis users noted impairment in verbal memory, attention, executive function and psychomotor function (Volkow, Swanson, Evins et al, 2016; Broyd, van Hell, Beale, Yucel & Solowij, 2016). However it should be noted that these studies focus on both chronic and acute effects rather than residual effects and sex differences were not reported. In a recent meta-analysis of fMRI studies of functionality in cannabis use the authors note few studies directly evaluate sex differences. (Blest-Hopley, Giampietro, & Bhattacharyya, 2018). In a review of the mechanisms of sex differences in cannabis users it was note that early onset schizophrenia and mood disorders appear to be related to functional differences in males and females with young females having a higher incidence as indicated by imaging studies (Calakos, Bhatt, Foster & Cosgrove, 2017).

**Sex differences in mood disorders and emotion processing**

In relation to emotion processing and emotion processing disorders there is a well-documented difference between males and females. Females generally show greater incidence of anxiety disorders compared to males who have a greater tendency towards substance abuse disorders (e.g. Kessler, McGonagle, Swartz, Blazer & Nelson, 1993; Kornstein et al., 1995; Schuch, Roest, Nolen, Penninx, & Jonge, 2014). Females show a greater incidence of anxiety disorders and fear and this increases as more variables are considered, for example extending from biological variables to include, trauma exposure, cognitive processing and environmental factors (McLean and Anderson, 2008). There are also well documented accounts of biological differences in emotion processing and emotion regulation (e.g. McClure, 2000; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; McKret & De Gelder, 2012) For example, women show an
increase in activity in amygdala in relation to cognitive reappraisal of emotion and a decrease in PFC activity (McRae et al, 2008)

**Cannabis, emotion and event related potentials**

The effects of residual cannabis use, evaluating cannabis users over time rather than administering cannabis acutely, has shown that cannabis does affect emotion processing (e.g. Troup et al., 2016; Troup, Andrzejewski, Braunwalder & Torrence, 2016; Troup, Torrence, Andrzejewski, & Braunwalder, 2017). In particular cannabis use effects event-related potentials (ERPs) associated with attention to emotion (Böcker et al., 2010; Theunissen et al., 2012; D'Souza et al., 2012). Negative emotions show an increase in P3 amplitudes in cannabis users. Positive emotions show a decrease in P3 amplitudes in relation to cannabis use. This is evident in particular for the implicit and empathic processing of emotional expression (Troup et al. 2016; Troup et al. 2017).

The limitations of a potentially stereotypical view of the possible effect of sex differences in emotion processing and as a consequence the effects on cannabis on emotion processing are highlighted by Brody (2010); arguing that there are exogenous social variables that should also be considered when looking at male female differences in emotion. However, investigation of these complex differences should not be neglected (McKret & DeGelder, 2012; Hodes, Walker, Labonté, Nestler, & Russo (2017) (in a recent mini review of sex differences in major mood disorder (MMD) in the relatively new field of epigenetics the authors stress that although current understanding of the biological basis for sex differences in human studies is not clear it is crucial that these potential differences are included for consideration (Hodes et al., 2017). Therefore, the current study aims to evaluate a data set from Troup et al., (2016) and Troup et al., (2017), to examine differences between sex and the effects of cannabis on emotion processing.
Method

Participants

Two-hundred and ninety-six undergraduate students recruited via the university’s psychological research participant pool provided informed consent and completed self-report demographics as well as the Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977) questionnaire for this study. 152 participants were excluded from the study due to incomplete questionnaires and missing/corrupt EEG data, leaving 144 participants, 80 females and 64 males. Mean score on the CESD was 19.69, with a cut off of 16 and above being considered elevated negative mood (Radloff, 1977). Participants reported no history of psychiatric or neurological disorder, and were not screened via urine or another measure for cannabis or other illicit/illegal drug use.

For compensation participants were provided Psychology course credit for their participation. This study was conducted under the approval of Colorado State University’s Office of Research Integrity & Compliance Review Office Institutional Review Board Protocol ID 12-3716H.

General Procedure

After assessments (CESD) and demographic data were completed, participants were fitted with an EEG cap. During EEG recording, participants sat approximately 30 cm away from a Dell desktop computer and were asked to complete a facial emotion-attention task. The task consisted of facial stimuli presentation involving four emotion conditions (neutral, happy, angry, and fearful) that comprised of faces obtained with permission from the Radbound Faces Database (Langner et al., 2010). These facial stimuli were presented pseudo-randomly within three attentional task conditions: implicit, explicit, and empathic; where participants were required to respond to the stimuli by either stating the sex of the face (implicit condition);
indicate the emotion expressed by the face (explicit condition) or to rate their empathy with the emotional expression displayed (empathic condition). A total of 32 faces were presented four times, representing the four emotional expressions, giving a total of 128 presentations. This was repeated for each of the three task condition with counterbalancing of expression and task between participants. Each trial consisted of 1500ms black screen followed by 1000ms of an image of a fixation cross on black background. Finally, 2000ms presentation of the randomly chosen facial expression. There was a 2000ms time window in which participants could respond (Troup et al., 2016; Troup et al., 2017) See Figure 1. Taken from Troup et al. (2016) and Troup et al. (2017), for a graphical representation of the task.

Figure 1
After completing the paradigm and EEG acquisition, cannabis use was then assessed by self-report via the Recreational Cannabis Use Evaluation (R-CUE); this questionnaire has been used in previous research investigating the relationship between cannabis and attentional emotional processing (Troup et al., 2016; Troup et al., 2017). To investigate the residual effects of cannabis participants who self-reported cannabis use in any form once a week or more were classified as heavy cannabis users, any self-reported cannabis use less than once a week classified the participant a casual user; these cut-offs are consistent with other previous cannabis use research (Blest-Hopley et al, 2018). Considering the nature of self-report, the diverse use of
cannabis in our sample, and focus on residual effects of cannabis, cannabinoid ratios of cannabis consumed were not recorded.

**EEG Acquisition**

EEG acquisition, as reported in previous research, was recorded via 25 Ag/AgCl electrodes mounted on a SynAmps2 64-channel QuickCap according to the 10-20 electrode placement system. Ground electrode site was midline anterior to Fz, online reference was right mastoid. A sampling rate of 500Hz and band pass of 0.1-50Hz with -200-1000ms epochs was implemented. Horizontal electro-oculogram was monitored using electrode placement on the outer canthi of the left and right eyes. Because of using the QuickCap system vertical electro-oculogram was recorded using electrodes FP1 and FP2 and recordings from these electrodes were included in our artifact rejection. Impedance was kept below 5 kΩ (Troup et al., 2016; Troup et al., 2017).

**Data Analysis**

EEG data was base-lined corrected to the pre-stimulus interval of -200 ms and re-referenced offline to the common average. Artifact rejection application was conducted using the built-in artifact rejection tool within the SCAN 4.5 EEG acquisition software; trials with an amplitude exceeding ±100 µV any electrode site resulted in analysis exclusion. Any participant who had all trials either rejected or absent for any one task condition was excluded from analysis. P1 mean amplitudes were calculated in the 80-100 ms epoch, P3 mean amplitudes were calculated in the 200-400 ms epoch. Analysis was conducted by forming four regions of interest (ROI): posterior left (PL) and right (PR) and anterior left (AL) and right (AR). These ROIs are informed by previous facial emotional-attention research (Troup et al 2016; Troup et al 2017), and consist of the following electrodes: P3/O1 (PL), P4/O2 (PR), F7/F3 (AL), and F8/F4 (AR).
In order to investigate differences in the task, sex, cannabis groups, and P1 and P3 mean amplitudes, a 3 (task) × 4 (emotion) × 4 (ROI) × 3 (cannabis groups) × 2 (sex) with CESD scores centered at the mean ($M = 19.50$) ANCOVA was used for P1 and P3 to determine the significance between factors, degrees of freedom were corrected with Greenhouse-Geisser. Bonferroni post-hoc tests were used when appropriate.

**Results**

**P1**

There was a significant interaction between Task × Emotion × ROI × Cannabis × Sex, $F(22.03, 1453.98) = 1.66, p = .028, \eta_p^2 = .025$. There were no differences in female cannabis groups. However, male non-users had enhanced P1 amplitudes in the PL compared to male casual users in explicit angry (non-users $M = 1.94, SE = 0.31$; casual $M = 0.81, SE = 0.26, p = .017$) and explicit fearful (non-users $M = 1.99, SE = 0.36$; casual $M = 0.84, SE = 0.29, p = .039$). Male heavy users ($M = -1.56, SE = 0.26$) had enhanced P1 amplitudes during empathy angry in the AR ROI compared to casual males ($M = -0.56, SE = 0.32; p = .049$). A summary of the results can be found in Table 1.
<table>
<thead>
<tr>
<th></th>
<th>Implicit</th>
<th>Explicit</th>
<th>Empathy</th>
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<tbody>
<tr>
<td></td>
<td>Non-users</td>
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<td>Heavy</td>
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<td>AR</td>
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<td>Note: Means and Standard Error for the P1 ERP with significant differences highlighted in grey. AL = Anterior Left, AR = Anterior Right, PL = Posterior Left, PR = Posterior Right, M = Males, F = Females</td>
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</table>
Sex differences in non-users. Males had enhanced P1 in implicit happy compared to females in PL, \( p = .046 \). Males also had enhanced P1 compared to females in explicit neutral (AL \( p = .033 \) and PR \( p = .034 \) ROIs), explicit happy (PL \( p = .048 \)), explicit angry (AR \( p = .030 \) and PL \( p = .001 \)), and explicit fear (PL \( p = .007 \)). In the empathy condition, males compared to females had enhanced P1 amplitudes for happy (AR \( p = .039 \)) and for fearful (PL \( p = .33 \)).

Sex differences in casual users. In the implicit condition, males, compared to females, had enhanced P1 amplitudes for happy (AL \( p = .034 \)) and angry (AR \( p = .006 \)). See Figure 2.

![Figure 2: Implicit Angry Anterior Right ROI](image)

**Figure 2.** P1 differences between male and female casual cannabis users for the implicit angry condition in the anterior right region of interest. Grey box roughly outlines the area P1 was calculated and the black box outlines the P3 component.

Sex differences in heavy users. In the implicit condition, males, compared to females, had enhanced P1 amplitudes in neutral (AL \( p = .001 \), AR \( p = .002 \), PL \( p = .006 \), and PR \( p =
SEX AND CANNABIS USE IN EMOTION PROCESSING

.008]), happy (AR \([p = .043]\) and PR \([p = .017]\)), angry (AR \([p = .040]\)), and fear (AL \([p = .011]\) and PL \([p = .049]\)). In the explicit condition, males, compared to females, had enhanced P1 amplitudes for angry (AL \([p = .036]\)) and fear (AR \([p = .037]\)). In the empathy condition, males, compared to females, had enhanced P1 amplitudes for neutral (AR \([p = .005]\), PL \([p = .015]\), and PR \([p = .022]\)), happy (AL \([p = .001]\), AR \([p = .038]\), and PR \([p = .006]\)), angry (AR \([p = .038]\) and PR \([p = .02]\)), and fear (AL \([p = .001]\) and PL \([p = .025]\)).

P3

Task*emotion*ROI*cannabis was significant, \(F(20.59, 1410.07) = 1.66, p = .031, \eta^2_p = .024\). There was a difference approaching significance in the empathy angry condition, non-users (\(M = -1.30, SE = 0.29\)) had more enhanced P3 compared to casual users (\(M = -0.36, SE = 0.26\)) in the anterior left, \(p = .052\). There was an interaction in task*emotion*ROI*cannabis*sex, \(F(20.59, 1410.07) = 1.72, p = .025, \eta^2_p = .025\). See table 2 for all means and standard errors.

Differences within sex. Among females, there were no differences in cannabis use. However, there was a difference in males. In the empathy, angry condition, male casual users (\(M = -0.108, SE = 0.40\)) had a diminished P3 compared to non-users (\(M = -1.65, SE = 0.49; p = .047\)), and approaching in heavy users (\(M = -1.32, SE = 0.32; p = .062\)) in the anterior right ROI (Figure 3).
Figure 3: This graph displays the difference in P3 amplitude between male casual users and non-users during the empathy angry trials. The black box shows the area in which P3 amplitudes were calculated.

Differences with cannabis

Non-users. Males had more enhanced P3 compared to females in the AR \( (p = .045) \), and the PL \( (p = .035) \) in the explicit neutral condition. In explicit angry, males had a more enhanced P3 than females in the PL, \( p = .044 \).

There was also differences in the empathy condition. In empathy fear, males had a more enhanced P3 than females in the PL, \( p = .044 \).

Casual users. There was significance in implicit angry, males had a more enhanced P3 than females in the AR, \( p = .017 \). (See Figure 2.)

Heavy users. Empathy neutral, males had more enhanced P3 in the AR \( (p = .013) \), and the PR \( (p = .026) \). Empathy happy, males had enhanced P3 in the AL \( (p = .013) \). See Figure 4.
Figure 4. P3 differences between male and female heavy cannabis users for the empathy happy condition in the anterior left region of interest. The black box outlines the area P3 was calculated.
### Table 2
Means and Standard Errors for P3

<table>
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**Note:** Means and Standard Error for the P3 ERP with significant differences highlighted in grey. AL = Anterior Left, AR = Anterior Right, PL = Posterior Left, PR = Posterior Right, M = Males, F = Females
**Discussion**

In sum our data suggests that there are complex differences in emotion processing based on between sex comparisons in relation to residual cannabis use patterns in both the P1 and P3 amplitudes. Differences in within sex groups in relation to cannabis use are only observed in males, showing differences for both P1 and P3 amplitudes. Male and female non-user groups both show patterns which become enhanced in cannabis use groups for P1 and P3. Between sex groups there were significant differences in the P1 amplitude. Male non-users having enhanced P1 amplitudes across emotion and task. In the casual use group again, males had enhanced P1 for implicit processing of negative and positive emotion. This enhanced P1 was even more distinct in the heavy male users compared to females. The P3 amplitude within groups appeared diminished for men. However, in relation to sex differences, as cannabis use increased so did the differences in P3 amplitude for males compared to females. The P3 was enhanced in males compared to females in relation to cannabis use groups. Between sex differences were subtler and, in some cases, only approaching significance. This pattern is consistent with previous ERP research, when not considering sex, in both emotion processing and the effects of cannabis on emotion processing (Böcker et al., 2010; Theunissen, et al., 2012; D'Souza, et al., 2012; Troup, et al., 2016 & Troup, et al., 2017).

These reported sex differences support the literature suggesting that males are more likely to report CUD whereas females are more likely to report emotion processing disorders when using cannabis literature (e.g. Kessler et al., 1993; Kornstein et al., 1995; Khan, et al., 2013; Schuch et al., 2014). Our data suggest that attention to emotion, as reflected in differences in ERPs associated with these processes, manifest differently between males and females in relation to cannabis use. Considering the literature showing male female differences in neurobiology, the brain structures affected by cannabis are also involved in emotion processing.
(e.g. Craft, 2005; Medina et al., 2007; Nagel et al., 2009; Fattore & Fratta, 2010; McQueeny et al., 2011) this would also fit with the pattern differences observed in our data.

Interestingly the P1 differences appear to be more robust in relation to cannabis use sex differences in comparison to the later occurring P3 component. This suggest that early attentional processes may be affected more in male cannabis users than females and that the pattern of sex differences in later processing as reflected in the P3 may be less clear.

Exploratory analysis of our data indicates that when controlling for mood using CESD scores male-female differences are reduced, particularly in the P3 component. This implies that the difference we are observing in males and females may be a result of biological difference in the prevalence of mood disorders (e.g. Kessler et al., 1993; Kornstein et al., 1995; McClure, 2000; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008; McKret & De Gelder, 2012; Khan et al., 2013; Schuch et al., 2014) as opposed to sex differences in the effects of cannabis use. It would seem that if this was the case we would expect to see differences in the P3 affected more by this as the P3 is associated with attention to emotion as an explicit process (Böcker et al., 2010; Theunissen et al., 2012; D’Souza et al., 2012; Troup et al., 2016 & Troup et al., 2017).

Despite these sex differences in human participants, research addressing these important differences are a consideration that warrants investigation and should not be ignored (McKret & DeGelder, 2012; Hodes et al 2017).

It is important to acknowledge that the population from which our data is sampled has been shown to be one with a high incidence of poor mental health, in particular mood disorders (e.g. Auerbach et al., 2016). Our limited control of other substance and psychiatric history of our participants beyond screening for subclinical mood disorders is a further limitation of this study. However, the ecological validity of residual cannabis use in post legalization populations
and the importance of noting these potential sex based differences warrant reporting of these effects even if they have limited interpretation.

**Conclusions**

The effects of cannabis use on sex and their relationship to emotion processing is complex. Differences in the ERPs associated with early visual attention in emotion processing (i.e. P1) between male and female were reported as well as a less robust but still evident difference in ERPs associated with later attentional processing of emotion (i.e. P3). These differences in brain responses quantified by ERPs warrant further investigation.
References


