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Residual effects of cannabis use on attentional bias towards fearful faces

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Abstract

Cannabis use has increased since legalization in various states within the United States of America. Although much of the research on the neurological and psychological effects of cannabis has been on non-human animals, the current research suggests that it can have anxiolytic effects and also decrease some cognitive functioning (e.g. memory, emotional processing, etc.). Individuals with high anxiety have been suggested to have increased attentional bias towards threat-related stimuli. The current study measured event-related potential (ERP) during a dot-probe task with fearful and neutral facial expression to examine the residual effects of cannabis use on attentional bias. The results indicated that there was reduced attentional bias, as measured by the P1 component in cannabis users, which is similar to low anxious individuals. Additionally, there was no difference between users and non-users in N170, indicating that the residual effects of cannabis did not interfere with face processing. However, an exploratory correlation indicated that higher cannabis use was associated with reduced N170 towards fearful faces. Cannabis use was associated with enhanced N2pc, which would indicate greater spatial orientation of attention. These results suggest that cannabis use did have an effect on attentional bias towards fearful faces.

Residual effects of cannabis use on attentional bias towards fearful faces

Although *Cannabis sativa* (cannabis, marijuana, weed, etc.) is currently federally illegal in the United States of America, 29 states and the District of Columbia have legalized medical use and 8 states and District of Columbia have legalized cannabis for both recreational and medical use (National Conference of State Legislatures, 2018). Cannabis use among individuals older than 12 years old has increased from 6.2% in 2002 to 8.3% in 2015 (Substance Abuse and Mental Health Services Administration, 2016). Cannabis has been suggested to have negative effects on memory, attention, executive function, and emotional processing (Broyd et al., 2016; Lovell et al., 2018; Troup et al., 2017, 2016b), and has also been correlated with differences in grey matter volume in areas of the brain involved in attention, emotion, and memory (Lorenzetti et al., 2016). Although there are some deficits correlated with cannabis use, some researchers have suggested that cannabinoids have anxiolytic effects (Berrendero and Maldonado, 2002; Patel and Hillard, 2006; Rubino et al., 2007; Viveros et al., 2005). Additionally, previous research has found that many cannabis users use cannabis to self-medicate for anxiety, depression, and PTSD (Crippa et al., 2009; Troup et al., 2016a). Anxiety symptoms, particularly social anxiety, has been related to an over attentional bias towards threat-related stimuli (Bar-Haim et al., 2007). Given the potential effect of cannabis on anxiety and that anxiety is associated with differences in attentional bias, this study examined attentional bias towards fearful faces in cannabis users using event-related potentials (ERPs).

The dot-probe task is a widely used method of studying attentional bias towards various stimuli (for review see van Rooijen et al., 2017) and examines differences between low and high anxiety (Bar-Haim et al., 2007). Typically, the dot-probe task displays a salient stimulus (fearful face) and a neutral stimulus (neutral face) simultaneously. Comparing the reaction time (RT) in

congruent trials (dot is spatially congruent with salient stimuli) and incongruent trials (dot is spatially incongruent with salient stimuli) allows an analysis of a general attentional bias.

However, Posner, Snyder, and Davidson (1980) suggested that there are three facets of attentional bias: orienting, engaging, and disengaging, which led to subsequent research including a baseline trial (two neutral stimuli or two salient stimuli) to examine the differences between orienting and delayed disengagement (Carlson & Reinke, 2008; Carlson, Reinke, & Habib, 2009; Carlson et al., 2011). Torrence, Wylie, and Carlson (2017) suggested that attention towards fearful faces is rapid but fleeting. That is, there is a rapid orientation towards the fearful face, but engagement to that location does not last long (< 300 ms). Despite the plethora of dot-probe research, current research has brought up serious and valid concerns of reliability of the dot-probe task when using RT (Price et al., 2015; Puls & Rothermund, 2017; Schmukle 2017; Staugaard, 2009); however, other research has suggested that alternative measures of attentional bias might be more reliable than RT such as eye-tracking (Price et al., 2015; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014), functional magnetic resonance imaging (fMRI) (White et al., 2016), and ERPs (Kappenman et al., 2015).

The amygdala is necessary for allocating attentional resources towards threat-related stimuli, as indicated by human lesion studies (Anderson & Phelps, 2001; Bach, Hurlemann, & Dolan, 2015). Similarly, fMRI research has indicated that amygdala is activated in attending towards positive and negative stimuli (Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; Hamann & Mao, 2002; Yang, Dong, Chen, & Zheng, 2012). Attentional bias has been associated with a network of brain areas including the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) and anterior insula (Carlson, Cha, & Mujica-parodi, 2013; Carlson, Reinke, & Habib, 2009; Fu, Taber-Thomas, & Pérez-Edgar, 2015; Liddell et al., 2005; Price et al., 2014;

White et al., 2016a). In the dot-probe task, amygdala activity has been correlated with activation in the visual cortex (Carlson et al., 2009) suggesting that the amygdala is involved in enhancing visual processing towards the salient stimuli. Previous research examining the neuroanatomical differences between cannabis users and non-users found alterations in grey matter in the amygdala, hippocampus, insula, orbital frontal cortex, and ACC (Hill et al., 2016; Lorenzetti et al., 2016). There is overlap in neural networks related to attentional bias and alterations in cannabis use.

To obtain timing information on attentional bias, researchers have used ERPs in the dot-probe task. Although there were some inconsistencies in the results, research using facial expression in the dot-probe task found that ERP components can detect attentional bias towards emotional facial expressions (Torrence and Troup, 2017). There are different ways to design the dot-probe task for ERP research. One way is to examine ERP components time-locked to the dot onset and therefore, there is no need to delay the dot after face offset. The second way is to examine the ERP components time-locked to face onset and therefore delaying the dot after face offset as to avoid stimulus overlap in the ERP signal. This study used the latter and will discuss the ERP components time-locked to face onset.

The P1 component has a positive peak occurring around 80-120 ms after stimulus onset in lateral occipital electrodes. Previous research indicated that P1 was enhanced when viewing a negative facial expression and has been suggested to originate in the posterior fusiform gyrus (Mueller et al., 2009; Pourtois et al., 2005). Enhancement of the P1 is thought to indicate increased attention to threat (Vuilleumier and Pourtois, 2007). The N170 component has a negative peak around 170 ms from the lateral posterior electrodes (Bentin et al., 1996). It was previously thought that the N170 was more enhanced for face vs. non-face objects and emotional

expression did not influence the N170 amplitude. However, a recent meta-analysis found that the N170 was more enhanced for emotional facial expressions than for neutral facial expressions (Hinojosa et al., 2015). Dot-probe studies have found that posterior-contralateral electrode to the negative facial expression had more negative N170 than the electrode ipsilateral to the negative face (Carlson and Reinke, 2010; Rossignol et al., 2013). Given that the N170 might reflect activation of the superior temporal sulcus (STS), occipital face area (OFA), and the fusiform face area (FFA) (Deffke et al., 2007; Herrmann et al., 2005; Itier and Taylor, 2004), the enhancement posterior-contralateral would indicate increased facial processing in that visual field. The N2 posterior-contralateral (N2pc) is a negative component peaking around 150-250 ms after stimulus onset in electrodes posterior-contralateral to the salient stimulus. Previous research suggested that the N2pc reflects initial orientation of spatial attention (Diao et al., 2017; Dowdall et al., 2012; Luck and Hillyard, 1994a, 1994b; Tan and Wyble, 2015).

ERP methods have been used in the dot-probe task to study differences between various forms of high anxiety and low anxiety (i.e. trait, social, and panic). Participants with high social anxiety had greater overall P1 amplitudes compared to participants with low social anxiety (Helfinstein et al., 2008). Additionally, Mueller et al. (2009) found that participants with social anxiety disorder had increased P1 amplitudes for angry-neutral trials compared to happy-neutral trials, which was not significant in low social anxiety participants. Another study found no group differences between high and low social anxiety in the N170 (Rossignol et al., 2013). However, enhanced N2pc towards angry faces was found in high social anxiety (Reutter et al., 2017) and trait anxiety (Fox et al., 2008).

Attentional bias towards threat-related stimuli has been suggested to be enhanced in high anxiety participants (Bar-Haim et al., 2007). A recent review found that ERP components can be

used to measure the increased attentional bias (Torrence and Troup, 2017). In addition, previous research suggested that cannabis use may be associated with self-medicating for anxiety (Crippa et al., 2009; Rubino et al., 2007), and might have anxiolytic effects (Berrendero and Maldonado, 2002; Patel and Hillard, 2006), but has also been associated with anxiogenic effects (Genn et al., 2004; Viveros et al., 2005). The purpose of this study was to examine if the residual effects of cannabis use was associated with a reduced attentional bias to fearful facial expressions using ERP. We predicted that cannabis users would exhibit reduced biases to fearful faces as measured by the P1, N170, and N2pc ERP components. A reduction in attentional bias could potentially be a mechanism of the anxiolytic effects of cannabis use or increased attentional bias as a mechanism for anxiogenic effects.

Method

Participants

Forty undergraduate students (24 females; ages 18 – 27, $M = 19.66$, $SD = 2.18$) from Colorado State University participated in this study. The participants were recruited from the psychology subject pool, which contains students enrolled in introduction to psychology and research methods. The participants received course credit for their participation. Thirty-nine participants were right handed. All had normal or corrected to normal vision in both eyes with no history of neurological or developmental disorders. The experiment was approved by Colorado State University Institutional Review Board.

Questionnaires

A personal inventory was used to determine age, vision, history of disorders, history of medicines used, etc. The Recreational Cannabis Use Questionnaire (RCUE; Troup et al., 2016) was used to measure cannabis use. The RCUE was developed to better understand cannabis use

among residents of Colorado and contains questions related to type of use (medical or recreational), method of use (inhalants, edibles, concentrates, transdermal, etc.), duration of use, frequency of use, and past use. The participants were divided into two groups: 20 users and 20 non-users. Previous research examined ERP related differences between social anxiety and controls using 16 and 18 participants, respectively (Mueller et al., 2009). Non-users were defined as having never used, whereas cannabis users were defined as using cannabis at least monthly for more than one year. We used this definition to remove participants that tried cannabis once or twice. Additionally, participants that used cannabis in the last 8 hours prior to the study were removed to examine residual rather than acute effects. The 8 hour cut off was based on previous research that defined the residual effects of cannabis (Blest-hopley et al., 2018). The RCUE was given to the participants after giving consent but before the task. This was to screen out participants that did not fall into user or non-user groups. The participants also completed the Center for Epidemiological Studies Depression (CESD; Radloff, 1997), the state portion of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), and PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013).

Dot-probe task

The task was programmed in Stim2 (Compumedics USA, Inc., Charlotte, NC, USA). The stimuli were displayed on a 20-inch PC monitor with a refresh rate of 60 Hz and a screen resolution of 1600×900 . The stimuli used in the dot-probe task were obtained from Gur et al. (2002): two female faces and two male faces. Each face had a fearful expression and a neutral expression. The facial expressions were grey scaled and a custom cropping tool was used to remove non-face stimuli (e.g. hair, background, etc.). The facial expressions were displayed on the left and right side of the computer screen. The faces subtended $5^\circ \times 7^\circ$ and were separated by

14° of the visual angle (7° from center of monitor) at 59 cm from the screen. The task was programmed for the presentation of faces at 50 ms, a delay of 500 ms, and the dot (1 cm in diameter) appearing until response (see Figure 1). There was a 2,000 ms inter-trial interval (Figure 1). The task consisted of three trial types: congruent (dot on same side of fearful face), incongruent (dot on opposite side of fearful face), and neutral-neutral (two neutral faces). There was a total of five blocks with 144 trials in each block (48 trials of each trial type), for a total of 720 trials (240 trials of each trial type). Previous ERP research have used similar total trial types (Mueller et al., 2009; Pourtois et al., 2004; Santesso et al., 2008). All trials were randomly presented within each block.

EEG collection

The EEG data were acquired using Curry 7 using 33 Ag/AgCl electrodes from a SynAmpsRT 64-channel QuickCap (Compumedics USA, Inc., Charlotte, NC, USA) using the 10-20 system. Ground was located between FZ and FPZ on the midline. The right mastoid was a reference during acquisition and the following electrodes were used for recording: FP1, FP2, F7, F3, FZ, F4, F8, FC5, FC1, FC2, FC6, T7, C3, CZ, C4, T8, CP5, CP1, CP2, CP6, P7, P3, PZ, P4, P8, PO7, PO3, POZ, PO4, PO8, O1, and O2. We used 32 scalp electrodes to adequately re-reference to an average reference. Horizontal electro-oculogram (HEO) electrodes were placed on the outer canthi of the left and right eye to detect saccades and eye blinks. Impedances were kept below 10 k Ω using electrolyte gel. Sampling rate was 500 Hz. The default recording bandwidth was from DC to 250 Hz.

ERP analysis

The EEG data was converted from Curry 7 format to EEGLAB format using the EEGLAB toolbox (Delorme and Makeig, 2004). ERPLAB (Lopez-Calderon and Luck, 2014)

was used for preprocessing and analyzing the data. The EEG data was re-referenced to the common average reference. The data was filtered with a bandpass of 0.1 to 40 Hz and epochs were extracted from -200 ms to 1000 ms (0 ms being face onset). A simple voltage threshold of -100 and 100 μ V were used to remove artifacts. The data were also visually inspected for motion artifacts. Participants were removed if more than 40% of one or more trial type were rejected. Mean amplitudes were analyzed for C1 (50 – 80 ms) and P1 (80 – 120 ms) (Suway et al., 2013) using O1 and O2 electrodes. Posterior-contralateral N170 (150 – 190 ms) (Carlson & Reinke, 2010) and N2pc (250 – 320 ms) (Holmes et al., 2014) components were analyzed from the P7 and P8 electrodes. All components were time-locked to face onset.

Data analysis

C1 and P1 amplitudes for trials that included fearful faces were analyzed between groups using an independent t-test. Electrodes O1 and O2 were averaged for analyses using independent t-tests. For posterior-contralateral N170 and N2pc, contralateral was defined as P7 fear right trials and P8 fear left trials averaged together and ipsilateral P7 fear left and P8 fear right trials averaged together. For the N170 and N2pc components, a mixed-factor ANOVA, 2 (users and non-users) $\times$ 2 (contralateral and ipsilateral) was used to determine differences in mean amplitude between groups and conditions. Bonferroni corrections were used when appropriate and for planned within group differences. All relevant measures, data, conditions, and exclusions are reported in this manuscript.

Results

One participant was removed because of too many rejected trials (70% rejected), leaving 39 participants. There were 20 non-users (15 females) and 19 users (9 females) (Table 1). There were no differences between groups in age, STAI, CES-D, or the PCL-5. The PCL-5 difference

approached significance, however, $t(36) = -1.67, p = .104, d = .459$. Cannabis users (one cannabis user did not complete the PCL-5) had a mean PCL-5 of 21.22 ($SD = 17.12$) and the non-users had a mean of 13.2 ($SD = 12.37$). None of the cannabis users indicated that they used cannabis in any form eight hours prior to the study. Four, however, indicated cannabis use 24 hours prior.

C1

There was no significant difference between users ($M = -0.23, SD = 0.81$) and non-users ($M = -0.11, SD = 0.97$) in C1, $t(37) = 0.40, p = .69, d = .134$ (Figure 2).

P1

There was a significant difference in P1 amplitude between cannabis users and non-users, $t(37) = 2.08, p = .044, d = .672$. Non-users ($M = 2.71, SE = 0.55$) had significantly greater P1 amplitude than cannabis users ($M = 1.36, SE = 0.33$) (Figure 2).

N170

There was a significant main effect for condition, $F(1, 37) = 17.11, p = .000, \eta_p^2 = .316$. Bonferroni post hoc comparisons indicated that contralateral electrodes ($M = -1.99, SE = 0.70$) had more negative amplitude than ipsilateral electrodes ($M = -1.71, SE = 0.70, p = .000$). There was not a significant interaction, $F(1, 37) = 0.68, p = .417, \eta_p^2 = .018$, indicating that there were no significant differences between users and non-users in contralateral and ipsilateral ($p > .200$). However, Bonferroni corrected planned comparisons within both groups suggested that in non-users, contralateral ($M = -1.53, SE = 0.54$) was more negative compared to ipsilateral ($M = -1.30, SE = 0.50, p = .023$). Within cannabis users, contralateral ($M = -2.46, SE = 0.55$) was also more negative compared to ipsilateral ($M = -2.11, SE = 0.51, p = .001$) (Figure 3).

N2pc

There was a significant main effect for condition, $F(1, 37) = 8.17, p = .007, \eta_p^2 = .181$. Bonferroni post hoc comparisons indicated that contralateral ($M = 0.94, SE = 0.28$) was more negative than ipsilateral ($M = 1.23, SE = 0.28, p = .007$). There was no significant interaction between groups and conditions, $F(1, 37) = 0.36, p = .553, \eta_p^2 = .01$, suggesting the neither condition was different between users and non-users. Within group, Bonferroni corrected planned analysis suggested that there was no significant difference between contralateral ($M = 0.81, SE = 0.39$) and ipsilateral ($M = 1.05, SE = 0.35, p = .114$) in non-users; however, contralateral ($M = 1.07, SE = 0.40$) was more negative than ipsilateral ($M = 1.45, SE = 0.36, p = .021$) in cannabis users (Figure 3). An independent t-test was used to explore group differences in difference score (contralateral – ipsilateral). Cannabis users ($M = -0.36, SD = 0.47$) were not different than non-users ($M = -0.23, SD = 0.77$), $t(37) = 0.60, p = .553, d = .204$.

Exploratory Analysis

An exploratory correlation analysis was conducted examining the relationship between N170 difference (contralateral minus ipsilateral) and reported monthly use. There was a significant positive correlation between N170 difference and monthly use, $R^2 = .236, F(1, 17) = 5.26, p = .035$ (Figure 3). No other ERP component was correlated with monthly use. The correlations for each component were not corrected for multiple comparisons and should be taken with caution. Additionally, uncorrected for multiple comparisons, STAI was neither correlated with monthly use nor the ERP components (within groups and overall). We also conducted an exploratory analysis to examine sex differences. The same analyses for cannabis use was used between males and females (ignoring cannabis use) and the results yielded no significant differences between sex in the ERP components.

Discussion

The ERP results indicated that there were differences between cannabis user and non-users in their response to fearful faces in the dot probe task. Specifically, non-users had greater P1 amplitudes than users in response to fearful faces. Greater P1 amplitude towards threat-related facial expressions has been associated with anxiety (Mueller et al., 2009). Both groups had differences in between contralateral and ipsilateral N170, indicating that both groups had enhanced face processing to the fearful facial expression. However, there was a correlation between monthly cannabis use and N170 difference. That is, the more frequent cannabis users had reduced difference between the contralateral and ipsilateral N170. Only cannabis users had differences in N2pc, which would suggest cannabis users had greater orientation towards the fearful facial expression.

Although N2pc showed an attentional bias towards fearful faces, the P1 data suggested that cannabis users had reduced attention towards fearful faces compared to non-users. Previous research found that individuals with low social anxiety had reduced P1 amplitudes when a negative facial expression was present as compared to high social anxiety individuals (Helfinstein et al., 2008). Enhanced P1 amplitude towards threat-related facial expressions is thought to reflect increased processing in the visual cortex modulated by the amygdala (Carlson et al., 2009; Pourtois et al., 2004). Even though this study found no correlations with state anxiety, the results did suggest that residual effects of cannabis were related to decreases in initial attention to fearful faces. This could suggest a mechanism of how cannabis can have anxiolytic effects via early attention modulation.

The significant main effect of condition is consistent with previous research that suggested enhanced N170 amplitudes posterior-contralateral to the threat-related facial expression (Carlson and Reinke, 2010; Rossignol et al., 2013). There were no group differences

in N170 amplitude, but each group had differences between contralateral and ipsilateral response amplitude. The group differences in N170 could be driven by the difference in P1. Given that both groups had attentional bias towards the fearful face, this may indicate that there were no differences between cannabis users and non-users in processing the fearful facial expression. However, a within cannabis group correlation revealed that more cannabis used per month was associated with reduced differences in contralateral and ipsilateral N170 amplitude. That is, heavier users had reduced processing of the fearful facial expressions compared to neutral expressions. A recent review suggested that the N170 was not different between patients with social anxiety and controls when the participants viewed emotional facial expressions (Harrewijn et al., 2017). Similarly, in the dot-probe task, Rossignol et al. (2013) suggested that fear of negative evaluation, a component of social anxiety, had no effect on N170 amplitude in contralateral electrodes. The enhanced contralateral N170 may reflect increased processing of the fearful facial expression in the contralateral STS but may not reflect the hypervigilance seen in anxiety (Harrewijn et al., 2017).

Since the N170 may not be related to increased attentional bias in anxiety, an alternative explanation is that increased cannabis use is associated with decreased emotional processing of facial expression. A recent study by Brooks and Brenner (2017) suggested non-users had enhanced N170 amplitudes to faces compared to heavy cannabis users (more than once a week) and moderate users (once or twice a month), but there were no statistical differences between cannabis groups. Additionally, these researchers found that the attenuated N170 in cannabis users was similar to individuals with high schizotypal personality traits in that there was reduced N170 amplitudes to faces compared to controls. The results of this study builds upon the results

of Brooks and Brenner (2017) that heavy cannabis use is associated with attenuated N170 towards fearful facial expressions.

Unlike posterior-contralateral N170, this study only found differences in N2pc within cannabis users, although there was a trend in non-users. The N2pc is thought to reflect an initial shift in orientation towards a salient stimuli (Diao et al., 2017; Dowdall et al., 2012; Luck and Hillyard, 1994a, 1994b; Tan and Wyble, 2015). Furthermore, the N2pc has been correlated with increased theta oscillations towards angry facial expressions in a dot-probe task (Diao et al., 2017). Maratos, Mogg, Bradley, Rippon, and Senior (2009) used magnetoencephalography (MEG) to study theta oscillations in the amygdala while the participants examined blurry and normal emotional facial expression. The researchers suggested that there were increased theta oscillations in the amygdala in blurry threat-related faces compared to neutral. Additionally, theta oscillations were found in the primary visual cortex and frontal cortex 50 to 250 ms after stimulus onset. Reutter et al. (2017) found enhanced N2pc correlated with increased social anxiety. Assuming the N2pc reflects theta oscillations in the visual cortex, which is mediated by theta oscillations in the amygdala, it is no surprise that fMRI research has found hyperactivation of the amygdala when viewing negative facial expressions in patients with generalized social phobia (Phan et al., 2006). In this current study, only cannabis users had enhanced N2pc amplitudes towards fearful faces, suggesting that unlike P1, cannabis users had increased attentional bias which resembles the finding in anxiety disorders (Bar-Haim et al. 2007). However, frequency of use had no relationship with N2pc difference scores (contralateral minus ipsilateral).

Alterations in attentional bias may be a mechanism of how cannabis can have anxiolytic effects. Previous research suggested that individuals with low anxiety have less attentional bias

towards threat-related stimuli compared to individuals with high anxiety (Bar-Haim et al., 2007). Attention bias modification training (training attention away from threat) could be a potential route to reducing anxiety related symptoms (Mogg, Waters, & Bradley, 2017). Cannabis may also reduce initial attentional response and face processing, but it does not affect spatial orientation of attention. Although selecting anxiety groups within cannabis users and non-users was outside the scope of this study, future research could select individuals with high or low anxiety that use cannabis to determine if a reduction in attentional bias is associated with reduced anxiety.

Although this study found that cannabis use was associated with reduced attention towards fearful facial expression, there were limitations. Examining ERPs time-locked to the probe would not have been reliable since there was a 500 ms delay from face offset to dot onset. Behavioral research has suggested that 300 ms after face onset, attention is no longer allocated to the location of the fearful face (Torrence et al., 2017). P1 time-locked to the probe has been used to examine engagement to an attended location. In congruent trials, the amplitude for P1 is more than for incongruent. Pourtois et al. (2005) conducted a source analysis for P1 and they suggested that for congruent trials, P1 was associated with posterior parietal and inferior temporal cortices, whereas incongruent trials were associated with anterior cingulate cortex. Given that some research has suggested anxiety is also related to a delayed disengagement and rapid orientation (Fox et al., 2002), examining P1 time-locked to the probe would add to these current findings. Additionally, we did not find a wide range of frequency of cannabis use in our sample. Future research could select different groups of heavy, moderate, and seldom cannabis users. Given that high cannabis use frequency has been associated with CB1 desensitization and downregulation (Lazenka and Selley, 2013), it is possible that heavy, longterm users would

experience more anxiety and have greater attentional bias towards threat-related stimuli.

Another limitation was that the ratio of men to women were different between cannabis users and non-users in our sample. Previous research has suggested that there are behavioral and ERP related differences in attentional bias between males and females (see Torrence & Troup, 2017).

A final caution in interpretation of the current results is the inability to eliminate the possibility that other unmeasured factors that differ between non-users and users could mediate the findings. For example, mood and anxiety disorders may be higher among those who use, and may independently be related to attentional bias changes (e.g., Bar-Haim et al. 2007). Although we did not observe differences between the two groups in the STAI or CES-D measures, we did not comprehensively screen for the presence of all mental illness in the participants. Future research could address this problem by using structured clinical interviews and/or a more comprehensive set of symptom rating scales.

This study was the first to examine the effects of residual cannabis use on attentional bias towards facial expressions using ERPs. The results suggested that there was a reduction in early attentional response to fearful faces, as measured by P1, in cannabis users. Frequency of cannabis use was also associated with reduced processing of fearful faces, measured by N170. However, cannabis use was associated with increased attentional bias towards fearful facial expression in N2pc, whereas non-users exhibited no differences. Given that neuroanatomical differences within the attentional bias network have been correlated with cannabis use in users (Lorenzetti et al., 2016), our results are suggestive of functional differences in attentional bias towards threat-related stimuli.

References

- Anderson, A.K., Phelps, E.A., 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 411, 305–9. <https://doi.org/10.1038/35077083>
- Bach, D.R., Hurlemann, R., Dolan, R.J., 2015. Impaired threat prioritisation after selective bilateral amygdala lesions. *Cortex* 63, 206–213. <https://doi.org/10.1016/j.cortex.2014.08.017>
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol. Bull.* 133, 1–24. <https://doi.org/10.1037/0033-2909.133.1.1>
- Bentin, S., Allison, T., Puce, A., Perez, E., McCarthy, G., 1996. Electrophysiological studies of face perception in humans. *J. Cogn. Neurosci.* 8, 551–565. <https://doi.org/10.1162/jocn.1996.8.6.551>
- Berrendero, F., Maldonado, R., 2002. Involvement of the opioid system in the anxiolytic-like effects induced by Δ^9 -tetrahydrocannabinol. *Psychopharmacology (Berl)*. 163, 111–117. <https://doi.org/10.1007/s00213-002-1144-9>
- Blest-hopley, G., Giampietro, V., Bhattacharyya, S., 2018. Neuroscience and Biobehavioral Reviews Residual effects of cannabis use in adolescent and adult brains — A meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev.* 88, 26–41. <https://doi.org/10.1016/j.neubiorev.2018.03.008>
- Brooks, G.A., Brenner, C.A., 2017. Is there a common vulnerability in cannabis phenomenology and schizotypy? The role of the N170 ERP. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2017.11.019>
- Broyd, S.J., Van Hell, H.H., Beale, C., Yücel, M., Solowij, N., 2016. Acute and chronic effects

- of cannabinoids on human cognition - A systematic review. *Biol. Psychiatry* 79, 557–567.
<https://doi.org/10.1016/j.biopsych.2015.12.002>
- Carlson, J.M., Cha, J., Mujica-parodi, L.R., 2013. Functional and structural amygdala e Anterior cingulate connectivity correlates with attentional bias to masked fearful faces. *CORTEX* 49, 2595–2600. <https://doi.org/10.1016/j.cortex.2013.07.008>
- Carlson, J.M., Reinke, K.S., 2010. Spatial attention-related modulation of the N170 by backward masked fearful faces. *Brain Cogn.* 73, 20–27. <https://doi.org/10.1016/j.bandc.2010.01.007>
- Carlson, J.M., Reinke, K.S., 2008. Masked fearful faces modulate the orienting of covert spatial attention. *Emotion* 8, 522–529. <https://doi.org/10.1037/a0012653>
- Carlson, J.M., Reinke, K.S., Habib, R., 2009. A left amygdala mediated network for rapid orienting to masked fearful faces. *Neuropsychologia* 47, 1386–1389.
<https://doi.org/10.1016/j.neuropsychologia.2009.01.026>
- Carlson, J.M., Reinke, K.S., LaMontagne, P.J., Habib, R., 2011. Backward masked fearful faces enhance contralateral occipital cortical activity for visual targets within the spotlight of attention. *Soc. Cogn. Affect. Neurosci.* 6, 639–645. <https://doi.org/10.1093/scan/nsq076>
- Crippa, J.A.S., Zuardi, A.W., Martin-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P.K., Fusar-Poli, P., 2009. Cannabis and anxiety: A critical review of the evidence. *Hum. Psychopharmacol.* 62, 11–14. <https://doi.org/10.1002/hup.1048>
- Deffke, I., Sander, T., Heidenreich, J., Sommer, W., Curio, G., Trahms, L., Lueschow, A., 2007. MEG/EEG sources of the 170-ms response to faces are co-localized in the fusiform gyrus. *Neuroimage* 35, 1495–1501. <https://doi.org/10.1016/j.neuroimage.2007.01.034>
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21.

<https://doi.org/10.1016/j.jneumeth.2003.10.009>

Diao, L., Qi, S., Xu, M., Fan, L., Yang, D., 2017. Electroencephalographic theta oscillatory dynamics reveal attentional bias to angry faces. *Neurosci. Lett.* 656, 31–36.

<https://doi.org/10.1016/j.neulet.2017.06.047>

Dowdall, J.R., Luczak, A., Tata, M.S., 2012. Temporal variability of the N2pc during efficient and inefficient visual search. *Neuropsychologia* 50, 2442–2453.

<https://doi.org/10.1016/j.neuropsychologia.2012.06.015>

Fox, E., Derakshan, N., Shoker, L., 2008. Trait anxiety modulates the electrophysiological indices of rapid spatial orienting towards angry faces. *Neuroreport* 19, 259–263.

<https://doi.org/10.1097/WNR.0b013e3282f53d2a>

Fox, E., Russo, R., Dutton, K., 2002. Attentional bias for threat: Evidence for delayed disengagement from emotional faces. *Cogn. Emot.* 16, 355–379.

<https://doi.org/10.1080/02699930143000527>

Fu, X., Taber-Thomas, B.C., Pérez-Edgar, K., 2015. Frontolimbic functioning during threat-related attention: Relations to early behavioral inhibition and anxiety in children. *Biol. Psychol.* 122, 98–109. <https://doi.org/10.1016/j.biopsycho.2015.08.010>

Genn, R.F., Tucci, S., Marco, E.M., Viveros, M.P., File, S.E., 2004. Unconditioned and conditioned anxiogenic effects of the cannabinoid receptor agonist CP 55,940 in the social interaction test. *Pharmacol. Biochem. Behav.* 77, 567–573.

<https://doi.org/10.1016/j.pbb.2003.12.019>

Gur, R.C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., Bajcsy, R., Posner, A., Gur, R.E., 2002. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *J. Neurosci. Methods* 115, 137–143.

Harrewijn, A., Schmidt, L.A., Westenberg, P.M., Tang, A., Van der Molen, M.J.W., 2017.

Electrocortical markers of information processing biases in social anxiety disorder: A review. *Biol. Psychol.* 129, 324–348. <https://doi.org/10.1016/j.biopsycho.2017.09.013>

Helfinstein, S.M., White, L.K., Bar-Haim, Y., Fox, N.A., 2008. Affective primes suppress attention bias to threat in socially anxious individuals. *Behav. Res. Ther.* 46, 799–810. <https://doi.org/10.1016/j.brat.2008.03.011>

Herrmann, M.J., Ehlis, A.-C., Muehlberger, A., Fallgatter, A.J., 2005. Source localization of early stages of face processing. *Brain Topogr.* 18, 77–85. <https://doi.org/10.1007/s10548-005-0277-7>

Hill, S.Y., Sharma, V., Jones, B.L., 2016. Psychiatry Research : Neuroimaging Lifetime use of cannabis from longitudinal assessments , cannabinoid receptor (CNR1) variation , and reduced volume of the right anterior cingulate. *Psychiatry Res. Neuroimaging* 255, 24–34. <https://doi.org/10.1016/j.psychresns.2016.05.009>

Hinojosa, J.A., Mercado, F., Carretié, L., 2015. N170 sensitivity to facial expression: A meta-analysis. *Neurosci. Biobehav. Rev.* 55, 498–509. <https://doi.org/10.1016/j.neubiorev.2015.06.002>

Holmes, A., Mogg, K., de Fockert, J., Nielsen, M.K., Bradley, B.P., 2014. Electrophysiological evidence for greater attention to threat when cognitive control resources are depleted. *Cogn. Affect. Behav. Neurosci.* 14, 827–35. <https://doi.org/10.3758/s13415-013-0212-4>

Itier, R.J., Taylor, M.J., 2004. Source analysis of the N170 to faces and objects. *Neuroreport* 15, 1261–1265. <https://doi.org/10.1097/01.wnr.0000127827.73576.d8>

Kappenman, E.S., MacNamara, A., Proudfit, G.H., 2015. Electrocortical evidence for rapid allocation of attention to threat in the dot-probe task. *Soc. Cogn. Affect. Neurosci.* 10, 577–

583. <https://doi.org/10.1093/scan/nsu098>
- Lazenka, M.F., Selley, D.E., 2013. Brain regional differences in CB1 receptor adaptation and regulation of transcription. *Life Sci.* 92, 446–452. <https://doi.org/10.1016/j.lfs.2012.08.023>
- Liddell, B.J., Brown, K.J., Kemp, A.H., Barton, M.J., Das, P., Peduto, A., Gordon, E., Williams, L.M., 2005. A direct brainstem-amygdala-cortical “alarm” system for subliminal signals of fear. *Neuroimage* 24, 235–243. <https://doi.org/10.1016/j.neuroimage.2004.08.016>
- Lopez-Calderon, J., Luck, S.J., 2014. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Front. Hum. Neurosci.* 8, 1–14. <https://doi.org/10.3389/fnhum.2014.00213>
- Lorenzetti, V., Solowij, N., Yücel, M., 2016. Review The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users Characteristics of Samples Included in Structural. *Biol. Psychiatry* 79, e17–e31. <https://doi.org/10.1016/j.biopsych.2015.11.013>
- Lovell, M.E., Bruno, R., Johnston, J., Matthews, A., McGregor, I., Allsop, D.J., Lintzeris, N., 2018. Addictive Behaviors Cognitive , physical , and mental health outcomes between long-term cannabis and tobacco users. *Addict. Behav.* 79, 178–188. <https://doi.org/10.1016/j.addbeh.2017.12.009>
- Luck, S.J., Hillyard, S.A., 1994a. Spatial filtering during visual search: Evidence from human electrophysiology. *J. Exp. Psychol. Hum. Percept. Perform.* 20, 1000–1014. <https://doi.org/http://dx.doi.org/10.1037/0096-1523.20.5.1000>
- Luck, S.J., Hillyard, S.A., 1994b. Electrophysiological correlates of feature analysis during visual search. *Psychophysiology*. <https://doi.org/10.1111/j.1469-8986.1994.tb02218.x>
- Maratos, F.A., Mogg, K., Bradley, B.P., Rippon, G., Senior, C., 2009. Coarse threat images reveal theta oscillations in the amygdala: A magnetoencephalography study. *Cogn. Affect.*

- Behav. Neurosci. 9, 133–143. <https://doi.org/10.3758/CABN.9.2.133>
- Mogg, K., Waters, A.M., Bradley, B.P., 2017. Attention bias modification (ABM): Review of effects of multisession ABM training on anxiety and threat-related attention in high-anxious individuals. Clin. Psychol. Sci. 1–20. <https://doi.org/10.1177/2167702617696359>
- Mueller, E.M., Hofmann, S.G., Santesso, D.L., Meuret, A.E., Bitran, S., Pizzagalli, D.A., 2009. Electrophysiological evidence of attentional biases in social anxiety disorder. Psychol. Med. 39, 1141–1152. <https://doi.org/10.1017/S0033291708004820>
- Patel, S., Hillard, C.J., 2006. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid. J. Pharmacol. Exp. ... 318, 304–311. <https://doi.org/10.1124/jpet.106.101287.pronounced>
- Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Tancer, M.E., 2006. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biol. Psychiatry 59, 424–429. <https://doi.org/10.1016/j.biopsych.2005.08.012>
- Posner, M.I., Snyder, C.R.R., Davidson, B.J., 1980. Attention and the detection of signals. J. Exp. Psychol. Gen. 109, 160–174. <https://doi.org/10.1037/0096-3445.109.2.160>
- Pourtois, G., Grandjean, D., Sander, D., Vuilleumier, P., 2004. Electrophysiological correlates of rapid spatial orienting towards fearful faces. Cereb. Cortex 14, 619–633. <https://doi.org/10.1093/cercor/bhh023>
- Pourtois, G., Thut, G., De Peralta, R.G., Michel, C., Vuilleumier, P., 2005. Two electrophysiological stages of spatial orienting towards fearful faces: Early temporo-parietal activation preceding gain control in extrastriate visual cortex. Neuroimage 26, 149–163. <https://doi.org/10.1016/j.neuroimage.2005.01.015>

- Price, R.B., Kuckertz, J.M., Siegle, G.J., Ladouceur, C.D., Silk, J.S., Ryan, N.D., Dahl, R.E., Amir, N., 2015. Empirical recommendations for improving the stability of the dot-probe task in clinical research. *Psychol Assess* 27, 365–376.
<https://doi.org/10.1037/pas0000036>. Empirical
- Price, R.B., Ph, D., Siegle, G.J., Ph, D., Silk, J.S., Ph, D., Cecile, D., Ph, D., Mcfarland, A., Dahl, R.E., Ryan, N.D., 2014. Looking under the hood of the dot-probe task: An fMRI study in anxious youth. *Depress Anxiety* 31, 178–187. <https://doi.org/10.1002/da.22255>.
- Puls, S., Rothermund, K., 2017. Attending to emotional expressions : no evidence for automatic capture in the dot-probe task 9931, 0–14. <https://doi.org/10.1080/02699931.2017.1314932>
- Reutter, M., Hewig, J., Wieser, M.J., Osinsky, R., 2017. The N2pc component reliably captures attentional bias in social anxiety. *Psychophysiology* 00. <https://doi.org/10.1111/psyp.12809>
- Rossignol, M., Campanella, S., Bissot, C., Philippot, P., 2013. Fear of negative evaluation and attentional bias for facial expressions: An event-related study. *Brain Cogn.* 82, 344–352.
<https://doi.org/10.1016/j.bandc.2013.05.008>
- Rubino, T., Sala, M., Viganò, D., Braida, D., Castiglioni, C., Limonta, V., Guidali, C., Realini, N., Parolaro, D., 2007. Cellular mechanisms underlying the anxiolytic effect of low doses of peripheral Δ^9 -tetrahydrocannabinol in rats. *Neuropsychopharmacology* 32, 2036–2045.
<https://doi.org/10.1038/sj.npp.1301330>
- Santesso, D.L., Meuret, A.E., Hofmann, S.G., Mueller, E.M., Ratner, K.G., Roesch, E.B., Pizzagalli, D.A., 2008. Electrophysiological correlates of spatial orienting towards angry faces: A source localization study. *Neuropsychologia* 46, 1338–1348.
<https://doi.org/10.1016/j.neuropsychologia.2007.12.013>
- Schmukle, S.C., 2005. Unreliability of the dot probe task. *Eur. J. Pers.* 19, 595–605.

<https://doi.org/10.1002/per.554>

Staugaard, S.R., 2009. Reliability of two versions of the dot-probe task using photographic faces.

Psychol. Sci. Q. 51, 339–350.

Suway, J.G., White, L.K., Vanderwert, R.E., Bar-Haim, Y., Pine, D.S., Fox, N.A., 2013.

Modification of threat-processing in non-anxious individuals: A preliminary behavioral and ERP study. J. Behav. Ther. Exp. Psychiatry 44, 285–292.

<https://doi.org/10.1016/j.jbtep.2012.11.006>

Tan, M., Wyble, B., 2015. Understanding how visual attention locks on to a location: Toward a computational model of the N2pc component. Psychophysiology 52, 199–213.

<https://doi.org/10.1111/psyp.12324>

Torrence, R.D., Troup, L.J., 2017. Event-related potentials of attentional bias toward faces in the dot-probe task: A systematic review. Psychophysiology e13051.

<https://doi.org/10.1111/psyp.13051>

Torrence, R.D., Wylie, E., Carlson, J.M., 2017. The time-course for the capture and hold of visuospatial attention by fearful and happy faces. J. Nonverbal Behav. 41, 139–153.

<https://doi.org/10.1007/s10919-016-0247-7>

Troup, L.J., Andrzejewski, J.A., Braunwalder, J.T., Torrence, R.D., 2016a. The relationship between cannabis use and measures of anxiety and depression in a sample of college campus cannabis users and non-users post state legalization in Colorado. PeerJ 4, e2782.

<https://doi.org/10.7717/peerj.2782>

Troup, L.J., Bastidas, S., Nguyen, M.T., Andrzejewski, J.A., Bowers, M., Nomi, J.S., 2016b. An event-related potential study on the effects of cannabis on emotion processing. PLoS One

11, 1–27. <https://doi.org/10.1371/journal.pone.0149764>

- Troup, L.J., Torrence, R.D., Andrzejewski, J.A., Braunwalder, J.T., 2017. Effects of cannabis use and subclinical depression on the P3 event-related potential in an emotion processing task. *Med. (United States)* 96, e6385. <https://doi.org/10.1097/MD.00000000000006385>
- van Rooijen, R., Ploeger, A., Kret, M.E., 2017. The dot-probe task to measure emotional attention: A suitable measure in comparative studies? *Psychon. Bull. Rev.* 42, 1686–1717. <https://doi.org/10.3758/s13423-016-1224-1>
- Viveros, M.P., Marco, E.M., File, S.E., 2005. Endocannabinoid system and stress and anxiety responses. *Pharmacol. Biochem. Behav.* 81, 331–342. <https://doi.org/10.1016/j.pbb.2005.01.029>
- Vuilleumier, P., Pourtois, G., 2007. Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia* 45, 174–194. <https://doi.org/10.1016/j.neuropsychologia.2006.06.003>
- Waechter, S., Nelson, A.L., Wright, C., Hyatt, A., Oakman, J., 2014. Measuring attentional bias to threat: Reliability of dot probe and eye movement indices. *Cognit. Ther. Res.* 38, 313–333. <https://doi.org/10.1007/s10608-013-9588-2>
- White, L.K., Britton, J.C., Sequeira, S., Ronkin, E.G., Chen, G., Bar-Haim, Y., Shechner, T., Ernst, M., Fox, N.A., Leibenluft, E., Pine, D.S., 2016. Behavioral and neural stability of attention bias to threat in healthy adolescents. *Neuroimage* 136, 84–93. <https://doi.org/10.1016/j.neuroimage.2016.04.058>

Figure 1: Dot-probe task

Figure 1: The dot-probe task used in this experiment. This is an example of a fear right, incongruent trial.

Table 1

Mean scores and standard deviations of age, STAI, CES-D, PCL-5, age of onset, and monthly use

	Cannabis users ($n = 19$)		Non-users ($n = 20$)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	19.84	2.34	19.5	2.06
STAI-State	40.78	7.99	37.68	11.25
CES-D	19.26	9.52	18	11.26
PCL-5	21.22	17.12	13.2	12.37
Age Onset	15.84	1.98	-	-
Monthly use	12.79	17.11	-	-

Note: There were no statistical significances between groups in age and questionnaires. PCL-5 was approaching significance, $p = .104$.

Figure 1: Event-related potentials waveform displaying C1 and P1 components. There was a significant difference in P1 between users and non-users, time window represented in the black box. There was no difference in C1 (grey box).

Figure 3: Event-related potentials waveforms elicited by fearful and neutral facial expressions.

The P7 and P8 electrodes were used to obtain contralateral and ipsilateral (contralateral means the electrode contralateral to the fearful face). Grey box represents area for the mean amplitude for N170 and the black box represents N2pc. UC = user contralateral, UI = user ipsilateral, NC = non-user contralateral, and NI = non-user ipsilateral.

Figure 4: Scatter plot displaying the positive correlation between difference scores of N170 (contralateral – ipsilateral) and average monthly use. Participants that reported more monthly use had less of a difference between contralateral and ipsilateral N170, indicating less attentional bias towards fearful faces.