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# 1 Impaired P100 among regular cannabis users in response to 2 magnocellular biased visual stimuli

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48

## ABSTRACT

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Regular cannabis using causes vision impairment by affecting human retinal neurotransmission. However, studies less considered its impact on the subsequent visual cortical processing, key feature for the integration of the visual signal in brain. We aimed at investigating this purpose in regular cannabis users using spatial frequencies and temporal frequencies filtered visual stimuli.

We recruited 45 regular cannabis users and 25 age-matched controls. We recorded visual evoked potentials during the projection of low spatial frequency (0.5 cycles/degree) or high spatial frequency gratings (15 cycles/degree), which were presented statically (0Hz) or dynamically (8Hz). We analyzed the amplitude, latency, and area under the curve of both P100 and N170, best EEG markers for early visual processing. Data were compared between groups by repeated measures ANCOVA.

Results showed a significant decrease in P100 amplitude among regular cannabis users in low spatial frequency ( $F(1,67)=4.43$ ;  $p=0.04$ ) and in dynamic condition ( $F(1,67)=4.35$  ;  $p=0.04$ ). Analysis showed a decrease in P100 area under the curve in regular cannabis users to low spatial frequency ( $F(1,67)=4.31$ ;  $p=0.04$ ) and in dynamic condition ( $F(1,67)=7.65$ ;  $p<0.01$ ). No effect was found on P100 latency, N170 amplitude, latency, or area under the curve.

We found alteration of P100 responses to low spatial frequency and dynamic stimuli in regular cannabis users. This result could be interpreted as a preferential magnocellular impairment where such deficit could be linked to glutamatergic dysfunction. As mentioned in the literature, visual and electrophysiological anomalies in schizophrenia are related to a magnocellular dysfunction. Further studies are needed to clarify electrophysiological deficits in both populations.

**Key words:** cannabis; EEG; Low Spatial Frequency; magnocellular; Visual Evoked Potentials ; P100

## I. INTRODUCTION

Cannabis is the third most frequently used drug worldwide after tobacco and alcohol and its regular consumption has numerous consequences on physical and mental health, notably with addiction and psychosis (Moore et al., 2007). Moreover, regular cannabis use has repercussions on cognition because it can impair verbal learning, memory, attention and executive functions (Broyd et al., 2016). Beside these effects on integrated cognitive functions, evidence is emerging concerning the impact of cannabis use at lower level, such as on early visual processing. As the endocannabinoid system is composed of ligands and both CB1 and CB2 receptors in animal and human retinas (Bouskila et al., 2016), our team found retinal dysfunctions in the ganglion cells (Schwitzer et al., 2017), the bipolar cells (Schwitzer et al., 2018) and the amacrine cells (Polli et al., 2020). Such retinal impairments thus raise questions about the subsequent stages of visual processing in the thalamus and the visual cortex.

It is interesting to note that the endocannabinoid system is involved in visual thalamus among several species, including humans (Herkenham et al., 1990). More precisely, cannabinoid receptors are expressed in the lateral geniculate nucleus (LGN) – the first ganglion relay of visual information (DeValois and DeValois, 1990). Animal studies have therefore shown the modulating role of the endocannabinoid system on LGN neuronal activity (Bouchard et al., 2016). Meanwhile, CB1 and CB2 receptors have been detected in the primary (V1) and the secondary (V2) visual cortex in animals and humans (Herkenham et al., 1990; Yoneda et al., 2013). Ohiorhenuan et al. (Ohiorhenuan et al., 2014) thus showed that a cannabinoid agonist could modify the functioning of V1 and V2 in primates. Although imaging and event-related potential studies support the idea of a visual cortical dysfunction related to regular cannabis use (Skosnik et al., 2006; Weinstein et al., 2008), less is known about the functional consequences of both thalamus and early cortical visual processing in regular cannabis users.

At subcortical and cortical levels, the visual system is anatomically and functionally segregated into different visual pathways. The subcortical magnocellular and parvocellular pathways begin in the retina and project, via the LGN, to different layers of V1 where the endocannabinoid

101 system is widely present (Glass et al., 1997; Sherman and Guillery, 2002). Functionally, these layers  
102 are involved in the encoding of visual images by separately processing spatial frequency and temporal  
103 frequency information (Derrington and Lennie, 1984). Indeed, the magnocellular pathway is  
104 preferentially sensitive to low spatial frequencies and movement, while the parvocellular pathway is  
105 preferentially sensitive to high spatial frequencies, but not to movement (Milner and Goodale, 2008).  
106 Spatial frequencies and movements can therefore be used to bias visual processing toward  
107 magnocellular or parvocellular pathways, although it should be noted that these characteristics cannot  
108 specifically select one path over the other (Skottun, 2015). In a human behavioral study, Lalanne et al.  
109 (Lalanne et al., 2017) showed that the contrast sensitivity to low spatial frequency (LSF) gratings of  
110 regular cannabis users with early-onset consumption was impaired compared to controls. This result  
111 could be interpreted as an effect of a regular cannabis use on magnocellular visual processing.  
112 However, the effect of regular cannabis use remains unclear in terms of the localization and timing of  
113 potential deficits in visual cortical processing. This issue should now be explored with EEG recording.

114 Visual event-related potentials constitute a direct approach that provides information about the  
115 neural functioning of the visual system. P100 and N170 are respectively generated in the occipito-  
116 temporal and parieto-temporal regions (Bötzel et al., 1995). They mainly reflect the primary visual  
117 cortex activity and are hence pertinent markers for early visual cortical processing in EEG. The  
118 endogenous N170 would be involved in high-level operations, for instance face processing while the  
119 exogenous P100 emphasizes low-levels characteristics (Rossion and Caharel, 2011). Additionally,  
120 P100 is associated with the global processing and initial stage of visual processing (Liu et al., 2002),  
121 would be sensitive to LSF and movements and can thereupon be considered as a marker of elementary  
122 stimulus feature processing (Pourtois et al., 2005). Based on these VEP characteristics, this study aims  
123 to investigate the early visual cortical processing across different spatial and temporal frequencies such  
124 as gratings in regular cannabis users compared to controls. Cognizant of the behavioral LSF deficit,  
125 we hypothesize that P100 in regular cannabis users would be especially altered in response to LSF  
126 stimuli. Since LSF are sensitive to movement (Tolhurst, 1973), we used both temporal frequencies  
127 (TF) : static (0Hz) and dynamic (8Hz) and postulated that such a decrease in P100 amplitude would be  
128 visible in dynamic conditions. Since Area Under the Curve (AUC) reflects cumulated amplitude

129 values, we assumed similar results between P100 AUC and P100 amplitude.

130

## 131 II. MATERIALS AND METHODS

### 132 2.1. Clinical assessments and participants ethic statement

133 We recruited participants from the general population from February 2014 to June 2016 as a  
134 part of the CAUSAMAP project (Cannabis USE And MAgnocellular Processing) which set out to  
135 study the neurotoxic effects of cannabis on human vision. We planned to match two cannabis users to  
136 one control, because of unknown variances and heterogenous performances. Both groups were age-  
137 and sex- matched. Not all EEG plots were usable due to artifacts in the recording. The final  
138 recruitment hence involved 45 regular cannabis users (n=45, mean  $age=25.13$  years,  $SD = 6.27$ ) and 25  
139 controls (n=25, mean  $age=25.6$  years,  $SD=5.68$ ). All participants were between 18 and 50 years old.  
140 They were medication-free except for contraceptives. They provided a detailed background of  
141 psychoactive medications and their medical history. All participants had a normal fundoscopic  
142 examination and normal or corrected-to-normal visual acuity verified by the Monoyer chart. They had  
143 no history of ophthalmic pathology, visual symptoms, eye infection, glaucoma, progressive retinal  
144 disease, or media opacity. They had a psychiatric assessment using the MINI 5.0 (Sheehan et al.,  
145 1998), and presented no current or past psychiatric disorders. Alcohol use was not an exclusion  
146 criterion to facilitate recruitment, but patients whose Alcohol Use Disorders Identification Test  
147 (AUDIT) indicated alcohol dependence were excluded. The inclusion criteria for regular cannabis  
148 users were a statement of at least 7 cannabis consumptions per week during the previous month, a  
149 positive urine-test for tetrahydrocannabinol, and a negative urine test (Nal von Minden) for cannabis,  
150 buprenorphine, benzodiazepines, cocaine, opiates, amphetamines, and methadone, plus abstinence  
151 from cannabis use for less than 12 hours to limit cognitive bias. The inclusion criteria for controls  
152 were no history of any illicit substance consumption, a negative urine test for tetrahydrocannabinol  
153 and no consumption of tobacco.

154 Participants received €100 in vouchers. They signed consent forms detailing all aspects of  
155 research in compliance with the Helsinki declaration (World Medical Association, 2013). All  
156 experiments were performed in accordance with the protection of persons committee of Nancy  
157 Regional University Hospital Center (2013-A00097-38 CPP 13.02.02). The study was registered on

158 [clinicaltrials.gov](https://clinicaltrials.gov) (ID NCT02864680).

## 159 **2.2. Visual stimuli and experimental procedure**

160 Stimuli were black and white sinusoidal vertical Gabor gratings and were presented at a size  
161 of 6 degrees of visual angle. We choose LSF and High Spatial Frequency (HSF) gratings  
162 corresponding to a SF of 0.5 cycles per degree (cpd) and 15cpd respectively, because these were better  
163 able to stimulate the magnocellular and parvocellular pathways (Butler et al., 2001). The gratings had  
164 a light/dark contrast of 80% and were presented against an isoluminant grey field. Both types of  
165 gratings were presented at two different TF conditions. In dynamic condition, black and white stripes  
166 alternated at a frequency of 8Hz. In static condition, the stripes did not alternate (0Hz). 20% of the  
167 stimuli were control stimuli at a contrast of 0% and were invisible. A total of five stimuli were used:  
168 LSF-static, LSF- dynamic, HSF-static, HSF-dynamic and control stimuli.

169 Figure 1 shows experimental procedure with both stimuli in LSF and HSF. Gratings were  
170 generated using the VSG system (Cambridge Research System). 300 stimuli were projected onto a  
171 CRT screen with a sampling rate of 120Hz, in an electrically shielded room with no surrounding light.  
172 The participants sat on a chair at a distance of 57 cm. During each trial, a central fixation cross was  
173 displayed during 500ms to 800ms and allowed participants to maintain their attention in the central  
174 zone of the screen. A randomized grating presentation was then centrally presented for 500ms. During  
175 the following blank screen lasting 1500ms, participants had to indicate via a response button if they  
176 had seen a grating, which also correspond to the behavior measure. Each trial was separated by a  
177 supplementary blank of 1500ms. The entire procedure consisted of 300 trials in total with 60 trials per  
178 stimulus condition and was divided into 2 blocks of 150 trials.

179 *[Insert Figure 1 here]*

## 180 **2.3. EEG recording and processing**

181 EEG recording was performed by Ag/AgCl electrodes using a 64-electrode Micromed<sup>®</sup>  
182 headset (10-10 system, QuickCap ; Compumedics Neuroscan<sup>®</sup>) referenced to both ear lobes. The  
183 signal was recorded at a sampling rate of 512 Hz (SD64 Headbox, Micromed<sup>®</sup>, Italy) with a  
184 bandwidth from 0.15Hz to 200Hz. Electrode impedances were kept below 10 k $\Omega$ . Vertical and

185 horizontal ocular electrodes were used for eye-artifact rejection. Each epoch was created with 1000ms  
186 pre-stimulus and lasted for 1000ms post-stimulus for each modality of SF relative to the stimulus  
187 onset. The data acquired were processed with Brain Vision Analyzer 2.0<sup>®</sup> software (Brain Products  
188 GmbH, Munich, Germany). The raw EEG signal was bandpass-filtered (0.5Hz-40Hz). Artifact  
189 rejection for noise, eyes blinking, muscular activity and non-biological component was performed  
190 using independent component analysis (ICA)(Jung et al., 2000). A manual artifact rejection was based  
191 on visual inspection to exclude the last remaining artifacts. Data collection focused on 3 pairs of  
192 interest electrodes in the left (O<sub>1</sub>, PO<sub>3</sub>, PO<sub>7</sub>) and the right hemisphere (O<sub>2</sub>, PO<sub>4</sub>, PO<sub>8</sub>). A grand average  
193 on all conditions determined the aspects of amplitude peaks. A root mean square (RMS) value  
194 calculation determined a temporal window for the extraction of each component amplitude.  
195 Consequently, the P100 and N170 amplitude peaks were extracted with intervals of 28ms and 38ms  
196 respectively around the maximum peak. Latencies were extracted based on their mean appearance on  
197 the grand average. Therefore, P100 latency was determined at 113ms for regular cannabis users and  
198 113ms for controls. N170 latency was determined at 184ms for regular cannabis users and 181ms for  
199 controls. Concerning AUC, BrainVision extracted the surface equal to the amplitude multiply by  
200 the latency around each maximum component peak.

201

## 202 **2.4. Statistical analysis**

203 The data were analyzed using STATISTICA 10 (Stat Soft Inc.). Both descriptive and  
204 comparative analyses were conducted according to the nature and distribution of the variables  
205 (normality assessed by Shapiro-Wilk test). Qualitative variables are described with frequencies and  
206 percentages ; quantitative variables were reported with the mean and SD (standard deviation). Since  
207 the sociodemographic and clinical characteristics followed a normal distribution given the non-  
208 significant Shapiro-Wilk test, the differences between groups were analyzed using an independent  
209 sample Student t-test. Given behavioral and EEG data followed a normal distribution, indicated by a  
210 non-significant Shapiro-Wilk test, and did not differ in variances following a non-significant. Levene  
211 test, we used parametric tests. Among cofounding factors, the relevant differences between groups

212 were years of education, AUDIT score, and number of alcohol uses per week. Education level had  
213 very little influence on a low-level visual task as SF perception, so it was not retained as a cofactor.  
214 AUDIT was strongly correlated with the number of alcohol uses per week and this latter was the most  
215 significant factor in the parametric tests. Thus, only the number of alcohols uses per week was retained  
216 as a continuous predictor. Behavioral data consisted of 2\*2 factors ANCOVA (TF [dynamic/static] x  
217 SF [LSF/HSF]). EEG variables were analyzed using 2\*3\*2\*2 factors ANCOVA (Hemisphere  
218 [left/right] x Electrodes [O<sub>1/2</sub>, PO<sub>3/4</sub>, PO<sub>7/8</sub>] x TF [dynamic/static] x SF [LSF/HSF]). We used a  
219 Greenhouse-Geisser correction to account for sphericity violations (Keselman and Rogan, 1980). A  
220 Fisher's Least Square Difference (LSD) test was used in post-hoc to specify differences between  
221 conditions. Pearson R- tests assessed correlations between experimental variables. For all tests, the  
222 significance was  $\alpha=0.05$ .

223

## 224 **2.5. Data availability statement**

225 The data are not publicly available due to information that could compromise the privacy of  
226 research participants. Nevertheless, for the verification of research results supporting the findings of  
227 this present study, raw EEG data and processed data are fully available from the corresponding author,  
228 upon reasonable request. Given EEG data were analyzed on BrainVision 2.0 software, raw EEG data  
229 and exported VEP characteristics can therefore be provided respectively in .trc and in .txt format or  
230 in .csv format with an anonymous participant code.

231

232

233

### III. RESULTS

234

#### 3.1. Population characteristics

235 Sociodemographic and clinical characteristics of the participants are summarized in Table 1.

236

*[Insert Table 1 here]*

237

238 Differences were noted concerning education ( $p < 0.05$ ), number of alcohols uses per week ( $p < 0.05$ )  
239 and AUDIT Score ( $p < 0.05$ ). Since cannabis is mixed in cigarettes, 38 of 45 regular cannabis users  
240 were tobacco smokers. None of them were tobacco dependent.

241

242

#### 3.2. Behavioral data

243 *[Supplementary Table 1 : Reaction time of participants between experimental conditions]*

244

245 Regular cannabis users and controls displayed respectively a mean reaction time of 434.94ms  
246 ( $SD = 93.17ms$ ) and 389.77ms ( $SD = 86.59ms$ ). The ANCOVA showed a significant main group effect  
247 ( $F(1,67) = 4.59$  ;  $p = 0.04$ ) indicating a longer reaction time in regular cannabis users than controls.  
248 Analysis did not mention an effect of the continuous predictor ( $F(1,67) = 0.65$  ;  $p = 0.42$ ). Analysis  
249 revealed a main SF effect ( $F(1,67) = 11.67$  ;  $\epsilon = 1.00$  ;  $p < 0.01$ ) explained by a shorter reaction time to  
250 LSF gratings ( $mean = 402.21ms$  ;  $SD = 31.24ms$ ) than HSF gratings ( $mean = 420.51ms$  ;  $SD =$   
251  $34.48ms$ ).

252

#### 3.3. Electrophysiological results

253 *[Supplementary Figure 1 & Supplementary Table 2 : EEG plots and Average VEP characteristics of*  
254 *participants across experimental conditions]*

255

256

##### 3.3.1. P100 amplitude

257 The mean P100 amplitude in regular cannabis users and controls was respectively 2.93 $\mu V$

258 ( $SD=1.59\mu V$ ) and  $3.81\mu V$  ( $SD=1.78\mu V$ ). ANCOVA showed a tendency concerning a main group  
259 effect ( $F(1,67)=3.82$  ;  $p=0.053$ ). We found no effect of the continuous predictor ( $F(1,67)=0.001$  ;  
260  $p=0.97$ ). A main hemisphere effect ( $F(1,67)=4.53$  ;  $\epsilon=1.00$  ;  $p=0.04$ ) highlighted a larger P100  
261 amplitude in the right hemisphere ( $mean = 3.55\mu V$  ;  $SD=1.70\mu V$ ) than the left hemisphere ( $mean =$   
262  $3.19\mu V$  ;  $SD = 1.43\mu V$ ). Analysis indicated a main electrodes effect ( $F(2,134)=48.42$  ;  
263  $\epsilon=0.98$  ;  $p<0.001$ ) explained by a greater P100 amplitude for O<sub>1</sub>/O<sub>2</sub> ( $mean = 4.25\mu V$  ;  $SD = 1.46\mu V$ )  
264 than PO<sub>3</sub>/PO<sub>7</sub> ( $mean = 2.61\mu V$  ;  $SD = 1.20\mu V$ ) or PO<sub>4</sub>/PO<sub>8</sub> ( $mean=3.27\mu V$  ;  $SD = 1.18\mu V$ ). A main SF  
265 effect was found ( $F(1,67) = 39.33$ ;  $\epsilon=1.00$  ;  $p<0.001$ ). The P100 amplitude was higher for LSF  
266 gratings ( $mean = 4.29\mu V$  ;  $SD = 1.66\mu V$ ) than HSF gratings ( $mean = 2.46\mu V$  ;  $SD = 1.68\mu V$ ). Most  
267 interestingly, ANCOVA revealed a SF\*Group interaction ( $F(1,67)=4.43$ ;  $\epsilon=1.00$  ;  $p=0.04$ ). Mean P100  
268 amplitude was significantly lower among regular cannabis users than controls in response to LSF  
269 gratings, as shown by a significant LSD Fisher test ( $p<0.01$ ) on LSF\*Group interaction (Figure 2).

270 *[Insert Figure 2 here]*

271  
272 A main TF effect ( $F(1,67)=6.32$  ;  $\epsilon=1.00$  ;  $p=0.01$ ) showed a greater P100 amplitude for dynamic  
273 gratings ( $mean = 3.52\mu V$  ;  $SD =1.46\mu V$ ) than static gratings ( $mean = 3.23\mu V$  ;  $SD = 1.53\mu V$ ). More,  
274 ANCOVA evidenced a significant TF\*Group interaction ( $F(1,67)=4.35$ ;  $\epsilon=1.00$  ;  $p=0.04$ ). The  
275 exploration of this interaction by LSD Fisher test mentioned that the mean P100 amplitude elicited by  
276 dynamic condition was significantly lower in regular cannabis users compared to controls ( $p<0.05$ ).  
277 This interaction is in Figure 3.

278 *[Insert Figure 3 here]*

279 Topographical maps of P100 activity across conditions in both groups is in Figure 4.

280 *[Insert Figure 4 here]*

281

### 282 **3.3.2. P100 Area Under the Curve (AUC)**

283 The mean P100 AUC of regular cannabis users and controls was respectively  $51.91 \mu V.ms$  ( $SD=39.17$   
284  $\mu V.ms$ ) and  $76.41\mu V.ms$  ( $SD=46.56 \mu V.ms$ ). ANCOVA analysis revealed a main group effect

285 ( $F(1,67)=4.23$  ;  $p=0.04$ ) highlighting a lower P100 AUC in regular cannabis users than controls. We  
286 found no effect of the continuous predictor ( $F(1,67)=0.11$ ;  $p=0.74$ ). A main electrodes effect  
287 ( $F(2,134)=43.99$  ;  $\epsilon=0.98$  ;  $p<0.001$ ) reported a larger P100 AUC for O<sub>1</sub>/O<sub>2</sub> ( $mean = 83.46\mu V.ms$  ;  
288  $SD=36.54\mu V.ms$ ) than PO<sub>3</sub>/PO<sub>7</sub> ( $mean= 45.91\mu V.ms$  ;  $SD =30.28\mu V.ms$ ) or PO<sub>4</sub>/PO<sub>8</sub> ( $mean =$   
289  $62.53\mu V.ms$  ;  $SD =28.77\mu V.ms$ ). Analysis exhibited a main SF effect ( $F(1,67)=51.25$  ;  $\epsilon=1.00$  ;  
290  $p<0.001$ ) explained by a greater P100 AUC for LSF gratings ( $mean = 94.90\mu V.ms$  ;  $SD=46.42\mu V.ms$ )  
291 than HSF gratings ( $mean = 33.04\mu V.ms$  ;  $SD =24.69\mu V.ms$ ). More importantly, ANCOVA highlighted  
292 a SF\*Group interaction ( $F(1,67)=4.31$ ;  $\epsilon=1.00$  ;  $p=0.04$ ) where mean P100 AUC was lower in regular  
293 cannabis users than controls in response to LSF gratings, as demonstrated a significant LSD Fisher test  
294 ( $p<0.01$ ). A main TF effect ( $F(1,67)=13.74$  ;  $\epsilon=1.00$  ;  $p<0.001$ ) indicated a higher P100 AUC for  
295 dynamic gratings ( $mean = 69.51\mu V.ms$  ;  $SD=36.59\mu V.ms$ ) than static gratings ( $mean=58.43\mu V.ms$  ;  
296  $SD=38.43\mu V.ms$ ). Besides, a TF\*Group interaction ( $F(1,67)=7.65$ ;  $\epsilon=1.00$  ;  $p<0.01$ ) reflected a lower  
297 P100 AUC in regular cannabis users compared to controls in dynamic conditions, as illustrated a  
298 significant LSD Fisher test ( $p<0.01$ ).

299

### 300 **3.3.3. P100 latency**

301 The mean P100 latency of regular cannabis users and controls was respectively 112.73ms  
302 ( $SD=5.14ms$ ) and 113.49ms ( $SD=5.11ms$ ). ANOVA analysis failed to show a main group effect  
303 ( $F(1,67)=0.11$  ;  $p=0.74$ ). We found no effect of the continuous predictor ( $F(1,67)=0.40$  ;  $p=0.53$ ). A  
304 main SF effect ( $F(1,67) = 10.64$  ;  $\epsilon=1.00$  ;  $p<0.01$ ) put in evidence a shorter P100 latency for LSF  
305 gratings ( $mean = 111.91ms$ ,  $SD =5.58ms$ ) compared to HSF gratings ( $mean = 114.23ms$ ,  $SD =$   
306  $5.43ms$ ). ANCOVA did not reveal any SF\*Group interaction ( $F(1,67)=2.8$ ;  $\epsilon=1.00$  ;  $p=0.10$ ) or any  
307 TF\*Group interaction ( $F(1,67)=2.72$ ;  $\epsilon=1.00$  ;  $p=0.10$ ).

308

### 309 **3.3.4. P100 correlations**

310 Correlations were measures to determine the influence of experimental and clinical factors. Pearson  
311 analysis showed a strong correlation between the mean P100 AUC and the mean P100 amplitude ( $r =$

312 0.97 ,  $p < 0.001$ ). The analysis failed to show any correlation between the mean P100 latency and the  
313 mean P100 AUC ( $r = 0.21$  ,  $p = 0.09$ ). Analysis did not mention any correlation between the mean P100  
314 amplitude, and the number of alcohol uses per week ( $r = -0.08$  ,  $p = 0.49$ ), or the number of cigarettes  
315 consumed daily ( $r = -0.12$  ;  $p = 0.33$ ) or the cannabis consumption in grams per week ( $r = -0.18$  ,  
316  $p = 0.24$ ).

317

### 318 **3.3.5. N170 Amplitude**

319 The mean N170 amplitude of regular cannabis users and controls was respectively  $-4.24\mu\text{V}$   
320 ( $SD = 2.93\mu\text{V}$ ) and  $-3.34\mu\text{V}$  ( $SD = 2.40\mu\text{V}$ ). ANCOVA failed to find any main group effect  
321 ( $F(1,67) = 0.78$ ;  $p = 0.38$ ). We found no effect of the continuous predictor ( $F(1,67) = 0.99$  ;  $p = 0.32$ ). A  
322 main SF effect ( $F(1,67) = 24.83$  ;  $\epsilon = 1.00$  ;  $p < 0.001$ ) indicated a larger N170 amplitude for HSF gratings  
323 ( $mean = -4.64\mu\text{V}$ ,  $SD = -2.79\mu\text{V}$ ) than LSF gratings ( $mean = -3.02\mu\text{V}$ ,  $SD = -2.25\mu\text{V}$ ). We found no  
324 SF\*Group interaction ( $F(1,67) = 0.54$ ;  $\epsilon = 1.00$  ;  $p = 0.47$ ) or TF\*Group interaction ( $F(1,67) = 2.10$ ;  
325  $\epsilon = 1.00$  ;  $p = 0.15$ ).

326

### 327 **3.3.6. N170 latency**

328 The mean N170 latency of regular cannabis users and controls was respectively 185.41ms  
329 ( $SD = 6.97\text{ms}$ ) and 182.69ms ( $SD = 7.18\text{ms}$ ). ANCOVA analysis failed to find any main group effect  
330 ( $F(1,67) = 3.09$  ;  $p = 0.08$ ). It did not find an effect of the continuous predictor ( $F(1,67) = 0.77$  ;  $p = 0.38$ ).  
331 Analysis indicated a main TF effect ( $F(1,67) = 15.80$  ;  $\epsilon = 1.00$  ;  $p < 0.001$ ) explained by a shorter N170  
332 latency for static gratings ( $mean = 182.26\text{ms}$ ,  $SD = 7.17\text{ms}$ ) than dynamic gratings ( $mean = 185.69\text{ms}$ ,  
333  $SD = 6.06\text{ms}$ ) . It did not reveal any SF\*Group interaction ( $F(1,67) = 0.12$ ;  $\epsilon = 1.00$  ;  $p = 0.73$ ) or  
334 TF\*Group interaction ( $F(1,67) = 1.33$  ;  $\epsilon = 1.00$  ;  $p = 0.25$ ).

335

### 336 **3.3.7. N170 AUC**

337 The mean N170 AUC of regular cannabis users and controls were respectively  $-106.02\mu\text{V.ms}$   
338 ( $SD = 101.96\mu\text{V.ms}$ ) and  $-68.91\mu\text{V.ms}$  ( $SD = 77.40\mu\text{V.ms}$ ). ANCOVA failed to find a main group effect

339 ( $F(1,67)= 1.34; p=0.25$ ) or an effect of the continuous predictor ( $F(1,67)=0.80 ; p=0.38$ ) . It did not  
340 reveal any SF\*Group interaction ( $F(1,67)=0.82; \epsilon=1.00 , p=0.37$ ) or TF\*Group interaction  
341 ( $F(1,67)=1.67 ; \epsilon=1.00 ;p=0.20$ ).

#### 342 IV. DISCUSSION

343 This study set out to compare early visual cortical processing in regular cannabis users and  
344 controls. Thus, we measured P100 and N170 responses thanks to LSF and HSF gratings presented  
345 statically or dynamically. We showed that regular cannabis users presented a decrease in both P100  
346 amplitude and P100 AUC, particularly to LSF and dynamic stimuli. We found no difference on P100  
347 latency or N170 amplitude, AUC, or latency. It is important to note that our stimulation method is  
348 consistent with the literature regarding controls. Indeed, P100 is primarily sensitive to LSF and  
349 dynamic information whereas N170 is thought to be more implicated in HSF and static information.

350 Our results complement the behavioral findings of Lalanne et al. (Lalanne et al., 2017). With  
351 similar gratings, regular cannabis users with early-onset consumption had a low-level visual  
352 deficiency, reflected by behavioral abnormalities exclusively on LSF gratings with 0.5cpd. Our results  
353 build on these previous findings by providing a physiological substrate to these behavioral results. **In  
354 our study, the decreased P100 amplitude in response to LSF and dynamic stimuli could be interpreted  
355 as a preferential magnocellular system alteration among regular cannabis users.** Indeed, although the  
356 P100 has been shown to arise from generator in the ventral and dorsal visual streams, this component  
357 seems to have a dorsal stream dominance reflected by the magnocellular pathway activity (Doniger et  
358 al., 2002; Javitt, 2009). Furthermore, while the parvocellular pathway is primarily sensitive to HSF  
359 and static information, the magnocellular pathway is thought to be involved in LSF, dynamic  
360 information and in movement processing by the modulation of dynamic TF condition (Livingstone and  
361 Hubel, 1988; Tootell et al., 1988). **At this stage, this preferential magnocellular alteration probably has  
362 no real impact on the vision of regular cannabis users. This potential deficit could nevertheless have  
363 consequences during complex visual tasks requiring the processing of moving images, such as driving,  
364 or during tasks involving the processing of spatial frequencies, such as distance vision or face  
365 perception.**

366           One possible explanation for such visual dysfunction could be due to the effect of  
367 cannabinoids on glutamatergic neurotransmission. In fact, cannabis ability to disrupt glutamate  
368 signaling is well demonstrated. For instance, high cannabis exposure induces an altered glutamate  
369 release by reducing the activity of glutamate enzymes such as glutamic acid decarboxylase and  
370 glutamine synthetase (Monnet-Tschudi et al., 2008). It also impairs long-term synaptic plasticity by  
371 altering the expression and function of AMPA and NMDA receptors and by disrupting the expression  
372 of glutamate transporters such as GLUT1 and GLAST (Chen et al., 2013; Fan et al., 2010; Good and  
373 Lupica, 2010).

374           It must be borne in mind that Schwitzer et al. (Schwitzer et al., 2017) indicated a delay in the  
375 retinal ganglion cell response shown by an increase in N95 pattern electroretinography implicit time.  
376 Since glutamate is one of the main neurotransmitters released by these cells during the retinal  
377 neurotransmission and because cannabis acts on the glutamatergic transmission in the central nervous  
378 system (Schwitzer et al., 2015; Wu and Maple, 1998), such retinal anomalies may be linked to  
379 dysfunctions in retinal glutamatergic transmission. As the retinal tracts projects through the LGN to  
380 the primary visual cortex (Sherman and Guillery, 2002), literature also mentions that a regular  
381 cannabis use tends to reduce the levels of glutamate-derived metabolites in both cortical and  
382 subcortical human brain regions (Colizzi et al., 2016). Our cortical anomalies could therefore be  
383 interpreted as a direct consequence of retinal impairment in regular cannabis users and share a  
384 common interpretation regarding a glutamatergic alteration. However, the current study does not  
385 provide a direct link between retinal and cortical damage. Further coupled ERG-EEG studies should  
386 give us more precise information about the location of this alteration.

387           These cortical dysfunctions could also be explained by the involvement of glutamate on the  
388 magnocellular system. Indeed, glutamate is present in the LGN synaptic terminals of several species,  
389 in higher proportions in the magnocellular system than in the parvocellular system (Montero and  
390 Zempel, 1986; Shaw and Cynader, 1986). Glutamate receptors such as NMDA and AMPA in the  
391 magnocellular system also play a very important role in the decrease of the visual response (Balducci  
392 et al., 2003; Kwon et al., 1992). More interestingly, it has been shown anatomically that the  
393 endocannabinoid system in the dorsal layers of the LGN could represent a site of neuromodulatory

394 action in normal vision. Indeed, the high level of CB1R in the dorsal magnocellular layers of the LGN  
395 could explain some of the behavioral effects of cannabinoids related to the integrity of the dorsal  
396 visual pathway, which is involved in visuo-spatial localization and motion perception (Javadi et al.,  
397 2015). All in all, one possible interpretation would be that regular cannabis use could generate  
398 disturbances in the magnocellular system and damage early visual processing.

399 Interestingly, cannabis use is associated with an increased risk factor of schizophrenia,  
400 particularly in early-age consumers (Moore et al., 2007; Arseneault et al., 2002). First, we note that our  
401 findings concerning magnocellular dysfunction are similar to those seen in this psychotic disorder  
402 (Kim et al., 2006; Martínez et al., 2012; Javitt, 2009). Second with P100 amplitude, Obayashi et al.  
403 (Obayashi et al., 2009) and Kim et al. (Kim et al., 2015) highlighted low-level visual information  
404 deficits to LSF in schizophrenia. More, Butler et al. (Butler et al., 2007) explored the  
405 neurophysiological correlates of such deficits by finding a P100 decrease in response to  
406 magnocellular-biased isolated check stimuli. Third, the glutamatergic system dysfunction in  
407 schizophrenia seems to be as pronounced as in regular cannabis users through differences in  
408 expression, function and receptors maturation (Falkenberg et al., 2014; Moghaddam and Javitt, 2012).  
409 All in all, these results indicate pervasive LSF integration and magnocellular dysfunctions, therefore  
410 impacting early visual processing in schizophrenia. Further studies in schizophrenia patients could  
411 reveal similar electrophysiological disorders to those of regular cannabis users and allow us to learn  
412 more about the mechanisms underlying the disease.

413 To the best of our knowledge, the present study is the first to investigate the impact of regular  
414 cannabis use on cortical SF processing using electrophysiological measurements. This technique  
415 provides objective and reproducible results, enables us to improve previous findings, and increases  
416 understanding of the cannabis impact at cortical level. Besides, there is also strong correspondence  
417 between the outcomes measured using both SF and TF biased stimuli.

418 The first limitation of our study was that a majority of our participants were tobacco users,  
419 which makes it difficult to draw conclusions about each compound. However, we do not find any  
420 correlations between cigarettes consumed daily and P100 amplitude. Moreover, it should be noted that  
421 smoking nicotine would not affect P100 amplitude in studies using visual modality tasks: in such case

422 only P100 latency is altered (Pritchard et al., 2003). Second, although the analysis found no effect of  
423 alcohol, this limitation must be considered because regular cannabis users consumed far more alcohol  
424 than controls. However, this continuous predictor has no effect on analysis. Further investigation of  
425 alcohol users without cannabis consumption could presumably address this question. Finally, it is  
426 extremely difficult to produce stimulation methods specific to the magnocellular system. First because  
427 our method of stimulation cannot specifically select one path over the other, but rather preferentially.  
428 Second, because V1 contains layers of magnocellular and parvocellular cells (4C alpha and 4C beta)  
429 (Callaway and Wiser, 1996), and the separation of both systems with a scalp EEG is quite unreachable.  
430 However, magnocellular system seems to be involved during low-contrast stimuli recording because  
431 of its projection mainly to the dorsal stream. The dissociation of the two systems can therefore be  
432 achieved with the stimuli used. Interpretation of results should be cautious and still require replication  
433 studies.

434

435

436

## V. CONCLUSION

437 In conclusion, we compared brain electrophysiological measurements in response to SF  
438 filtered gratings with different TF. Our results showed a decrease in both P100 amplitude, specifically  
439 to LSF and in dynamic conditions among regular cannabis users than controls. **These findings could be**  
440 **interpreted as preferential magnocellular dysfunction caused by impaired glutamatergic**  
441 **neurotransmission.** Our results bring to light interesting research perspectives on schizophrenia, a  
442 pathology apparently marked by physiological mechanisms similar to those encountered in regular  
443 cannabis users. Further electrophysiological studies could conceivably reveal common abnormalities  
444 in both populations and would enable us to better understand the onset of psychiatric illness, especially  
445 in populations with mental health disorders who use cannabis at a very young age.

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## VI. AUTHOR DISCLOSURES

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### 6.1. Role of the Funding Source

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### 6.2. Contributors

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### 6.3. Conflict of Interest

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471

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VL, JK, TS, LM and RS were responsible for the study concept and design. VL, JK, TS, LM, RS and FB contributed to the inclusion of participants, the completion of clinical evaluations and the acquisition of EEG data. VL, JK and IR performed the pre-processing and the processing of EEG data. VL, JK, EA, FL, LL, and IR assisted with data analysis and interpretation of findings. EA validated the results of the statistical analyses. IR drafted the manuscript. SBB provided critical revision of the manuscript for important intellectual content. All authors reviewed content and approved final version for publication.

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## VIII. FIGURE LEGENDS

657 **Figure 1.** Representation of the experimental procedure with both LSF and HSF gratings presented  
658 during the study.

659

660 **Figure 2.** Spatial Frequency\*Group interaction on P100 amplitude. Data were obtained from the  
661 average activity of the 3 pairs of interest electrodes (O<sub>1</sub>/O<sub>2</sub>, PO<sub>3</sub>/PO<sub>4</sub>, PO<sub>7</sub>/PO<sub>8</sub>) on LSF and HSF  
662 stimuli in both groups. The difference between LSF and HSF is significant. Means are displayed with  
663 their standard error (SEM).

664

665 **Figure 3.** Temporal Frequency\*Group interaction on P100 amplitude. Data were obtained from the  
666 average activity of the 3 pairs of interest electrodes (O<sub>1</sub>/O<sub>2</sub>, PO<sub>3</sub>/PO<sub>4</sub>, PO<sub>7</sub>/PO<sub>8</sub>) on Static and Dynamic  
667 conditions among both groups. The difference between dynamic condition and static condition is  
668 significant. Means are displayed with their standard error (SEM).

669

670 **Figure 4.** Topographical maps of P100 activity across experimental conditions in both groups.  
671 Subtraction of the topography between groups is shown by  $\Delta$  column. SF : Spatial Frequency ; TF :  
672 Temporal Frequency.

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674

## IX. TABLE AND TABLE LEGENDS

675 **Table 1. Sociodemographic and clinical characteristics of the participants.** Data are presented as  
 676 mean unless otherwise is indicated. Standard deviation is in brackets. n.s. : not significant, NA : not  
 677 applicable, AUDIT : Alcohol Use Disorders Identification Test score, CAST : Cannabis Abuse  
 678 Screening Test Score

	<b>Regular Cannabis Users (n=45)</b>	<b>Controls (n=25)</b>	<b>p value t-test</b>
Number of women/ Number of men (%)	10/35 (22/78)	6/19 (24/76)	n.s.
Age (years)	25.13 [6.27]	25.6 [5.68]	n.s.
Education (years)	13.27 [2.16]	14.88 [1.39]	<b>*p&lt;0.05</b>
AUDIT score	7.07 [4.74]	3.48 [2.84]	<b>*p&lt;0.05</b>
No. alcohol uses/week	7.32 [8.37]	1.92 [2.53]	<b>*p&lt;0.05</b>
Fagerström score	2.02 [2.20]	0 [0]	NA
No. cigarettes/day	6.74 [6.46]	0 [0]	NA
CAST score	4.09 [1.16]	0 [0]	NA
No. joints/week	26.04 [21.18]	0 [0]	NA
Grams of cannabis/week	5.30 [3.93]	0 [0]	NA
Age first cannabis use	15.80 [1.73]	0 [0]	NA
Cannabis use duration	9.33 [6.16]	0 [0]	NA

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