Anomalies fonctionnelles rétiniennes dans les troubles neuropsychiatriques et leurs liens avec les dysfonctionnements cérébraux

Thomas Schwitzer

UNIVERSITÉ DE LORRAINE

Ecole Doctorale BioSE (Biologie-Santé-Environnement)

Mémoire

Présenté pour la candidature au diplôme

D'HABILITATION A DIRIGER LES RECHERCHES

Par

Thomas SCHWITZER

ANOMALIES FONCTIONNELLES RETINIENNES DANS LES TROUBLES NEUROPSYCHIATRIQUES ET LEURS LIENS POTENTIELS AVEC LES DYSFONCTIONNEMENTS CEREBRAUX

(Discipline CNU 4903 : Psychiatrie d'adultes ; Addictologie)

Parrain Scientifique : Professeur Raymund Schwan
Professeur des Universités- Praticien Hospitalier
Université de Lorraine, Faculté de Médecine

Université de Lorraine

INSERM U1114, Neuropsychologie cognitive et physiopathologie de la schizophrénie

Centre Psychothérapique de Nancy

Nom-Prénom-âge	Thomas Schwitzer
Laboratoire de rattachement	INSERM U1114
Discipline de L'HDR	Psychiatrie d'adultes- Addictologie
Thèmes de recherche	Neuropsychiatrie, Rétine, Neurotransmission, Fonction rétinienne

Résumé

Un des obstacles majeurs de la recherche en neurosciences et en psychiatrie est la difficulté d'accéder de manière directe au fonctionnement du cerveau afin de comprendre les mécanismes biologiques à l'origine des dysfonctionnements cérébraux dans les troubles psychiatriques et addictifs. En tant qu'extension anatomique et développementale du système nerveux central, la rétine pourrait permettre d'offrir un accès indirect aux fonctions neurologiques cérébrales. Ainsi, l'investigation de la fonction rétinienne apporte l'unique opportunité d'étudier de manière objective un réseau neuronal complexe présentant des similarités avec celui du cerveau. Notre équipe s'est dans un premier temps intéressé à l'étude de la fonction rétinienne chez les usagers réguliers de cannabis chez lesquels nous avons montré des dysfonctionnements à plusieurs étages rétiniens et qui ont été observés avec des mesures électrophysiologiques basées sur l'électrorétinogramme. Ces résultats permettraient de préciser les modulations de la transmission synaptique cérébrale induites par l'usage régulier de cannabis. Ainsi, nous formulons l'hypothèse que les modifications de la fonction rétinienne peuvent être liées à des modifications spécifiques de neurotransmission cérébrale dans les troubles neuropsychiatriques. Actuellement, afin de valider ces hypothèses, nous évaluons la fonction rétinienne dans plusieurs troubles neuropsychiatriques comme le trouble dépressif majeur, la schizophrénie et l'usage régulier de tabac, d'alcool et de cannabis. Ces mesures pourraient à terme fournir des modèles de compréhension des anomalies de neurotransmission et fournir des marqueurs physiologiques fonctionnels dans le champ des troubles neuropsychiatriques et addictifs.

Abstract

One of major obstacles in neuroscience and psychiatry research is the difficulty of directly accessing the brain function to understand the biological mechanisms underlying brain dysfunctions in psychiatric and addictive disorders. As an anatomical and developmental extension of the central nervous system, the retina could afford to offer an indirect access to brain neurological functions. Investigating the retinal function provides the unique opportunity to study in an objective way a complex neuronal network which shares similar properties with the brain. Our team was initially interested in the study of retinal function in regular cannabis users in which we showed dysfunctions in several retinal stages and observed with electrophysiological measurements based on electroretinogram. These results could help to clarify the modulations of cerebral synaptic transmission induced by regular use of cannabis. Thus, we hypothesize that changes in retinal function may be related to specific changes in brain neurotransmission in neuropsychiatric disorders. Currently, in order to validate these hypotheses, we evaluate retinal function in several neuropsychiatric and addictive disorders such as major depressive disorder, schizophrenia and regular use of tobacco, alcohol and cannabis. These measures could eventually provide models for understanding neurotransmission anomalies and provide functional physiological markers in the field of neuropsychiatric and addictive disorders.

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Je remercie le Professeur Karine Angioi-Duprez pour son soutien constant et sans faille depuis nos premiers échanges, pour ses conseils toujours précieux, et pour la confiance qu'elle m'a témoignée.

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Je remercie tous les étudiants qui m'ont accordé leur confiance et qui sont cités dans ce travail.

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Activites d'encadrement ***74***

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5 publications representatives ***95***

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TITRES ET TRAVAUX

ETAT CIVIL

Thomas Schwitzer
Né le 11/09/1986 à Metz

Adresse professionnelle :

Centre Psychothérapique de Nancy-Laxou
Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy
1, rue du Dr Archambault
54 520 Laxou - France

Tel. Professionnel 03 83 92 84 40
Tel. Portable 06 85 17 30 41

Laboratoire :

INSERM U 1114
Neuropsychologie Cognitive et Physiopathologie de la Schizophrénie
Département de Psychiatrie
CHRU de Strasbourg
1, place de l'Hôpital
67 091 Strasbourg Cedex

DIPLOMES ET TITRES UNIVERSITAIRES

Diplôme d'Etat de Docteur en Médecine

2015 Thèse pour le diplôme de Docteur en Médecine, Université de Lorraine
Thèse « Pertinence des mesures électrophysiologiques rétiniennes dans le trouble dépressif majeur : une revue de littérature »
Directeur de thèse : Dr Vincent Laprévote

Diplômes d'Université

2017 DIU de Pédagogie et Simulation en Santé, Université de Lorraine
2015 DU d'Exploration de la fonction visuelle, Université Paris Diderot
2012 DU de Psychopathologie Périnatale, Université de Lorraine
2009 DU d'Expérimentation animale niveau 1, Université de Lorraine

Formation pédagogique

2017 DIU de Pédagogie et Simulation en Santé, Université de Lorraine
2016 Certification SIDES

Diplômes d'Etudes Spécialisées (DES ou DESC)

2016 Diplôme d'études spécialisées en Psychiatrie, Université de Lorraine
Mémoire : « Bases cliniques et neurobiologiques justifiant l'étude de la fonction visuelle chez les consommateurs de cannabis »
Directeur : Dr Vincent Laprévote

Clinicat ou Assistanat des Universités

11.2016 Chef de Clinique des Universités – Assistant des Hôpitaux
Présent Service de Psychiatrie d'Adultes, Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy, CPN Nancy-Laxou
Chef de service : Pr Raymund Schwan

DEA ou Master 2

2009 : Master 2 Professionnel d'Expertise préclinique des médicaments et Pharmacologie de Sécurité, Université de Lorraine, Faculté de Pharmacie
Mémoire : « Améliorer l'évaluation de la fonction cardiovasculaire par télémétrie en pharmacologie de sécurité : évaluation de la contractilité cardiaque par la pression ventriculaire gauche chez les espèces de non rongeurs »
Directeur : Dr Guillaume Froget

Thèse d'Université

2016 Thèse d'Université en Neurosciences, Ecole doctorale Biose, Biologie-Santé-Environnement, Université de Lorraine
Direction : Pr Raymund Schwan- Dr Vincent Laprévote- Dr Anne Giersch
« Evaluation de l'impact de l'usage régulier de cannabis sur le fonctionnement rétinien par la mesure de l'électrorétinogramme »

Soutenue le 07 novembre 2016 devant le jury suivant :
Pr Arthur Kaladjan (Rapporteur)
Pr Mircea Polosan (Rapporteur)
Pr Karine Angioi-Duprez (Présidente)
Pr Frédéric Limosin
Dr Benoit Trojak

DISTINCTIONS : PRIX, BOURSES…

Lauréat au Neuroethics Solutions for the Neurotechnology Industry, British Columbia University, Vancouver, Mars 2018

1er Prix de la Meilleure Publication de l'Année en Psychiatrie. 9ème Congrès Français de Psychiatrie, Lyon, 29 Novembre-2 Décembre 2017

3ème nominé du Prix Jeune Addictologie du Fonds Actions Addictions. 11e Congrès International de l'Albatros, Paris, 31 mai-2 Juin 2017

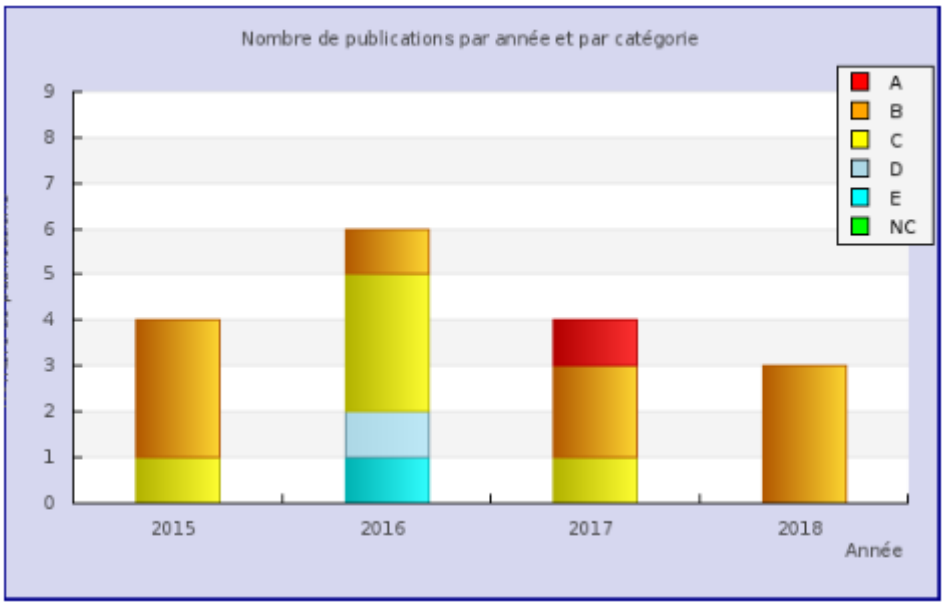
PUBLICATIONS

Bibliométrie au 16/01/2019

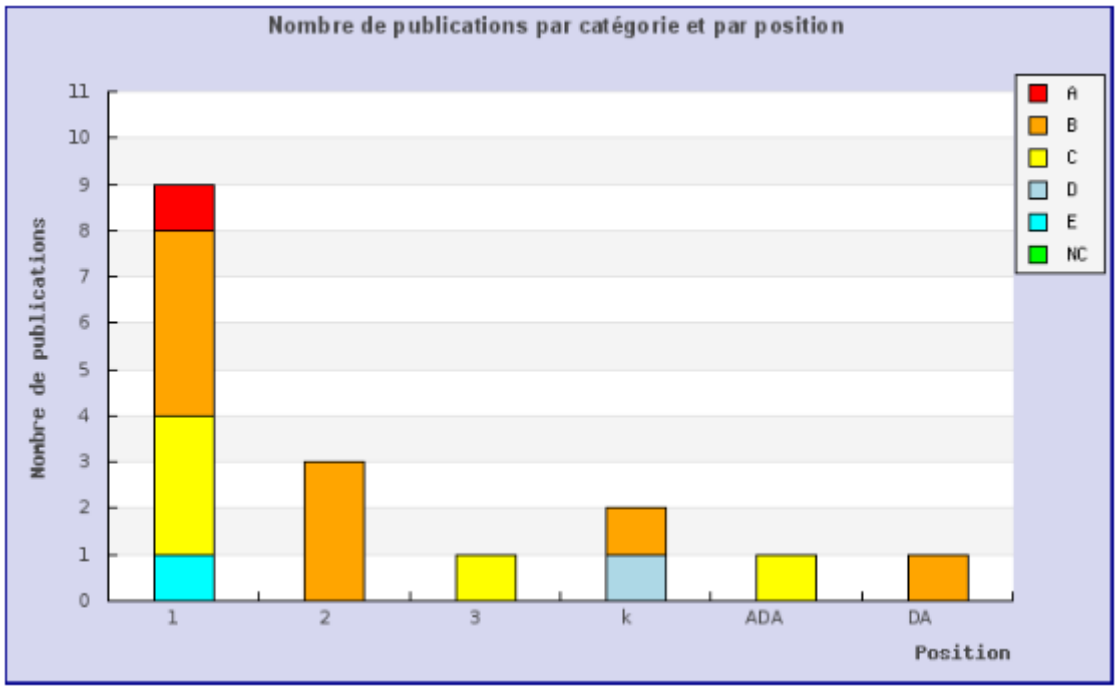
Publications indexées PubMed : 17 (19 en prenant en compte les deux publications sous presse)
Score SIGAPS : 291 (347 en prenant en compte les deux publications sous presse)
Indice H : 7 (Google Scholar)
Citations : 142 (Google Scholar)

Nombre total de points SIGAPS, répartition par catégorie et par année

Période : 2014 - 2019								
Année	**Total**	**A**	**B**	**C**	**D**	**E**	**NC**	**Score**
2014	0	0	0	0	0	0	0	0
2015	4	0	3	1	0	0	0	74
2016	6	0	1	3	1	1	0	77
2017	4	1	2	1	0	0	0	74
2018	3	0	3	0	0	0	0	66
2019	0	0	0	0	0	0	0	0
Total	**17**	**1**	**9**	**5**	**1**	**1**	**0**	**291**



Nombre publications par catégorie et par position



Publications dans des revues à comité de lecture référencées Pubmed

Schwitzer T, Henrion ML, Sarre D, Albuisson E, Angioi-Duprez K, Giersch A, Lalanne L, Schwan R, Laprevote V. Spatial localization of retinal anomalies in regular cannabis users: the relevance of the multifocal electroretinogram. Schizophrenia Research. In press (IF: 3.96)

Schwitzer T, Schwan R, Angioi-Duprez K, Lalanne L, Giersch A, Laprevote V. Cannabis use and human retina: the path for the study of brain synaptic transmission dysfunctions in cannabis users. Neuroscience and Biobehavioral Reviews. In press (IF: 8.04)

Lucas A, Thirion A, Schwan R, Krieg J, Angioi-Duprez K, Laprevote V, **Schwitzer T**. Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar 8;89:335-340 (IF: 4.18)

Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Lalanne L, Albuisson E, Laprevote V. Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: The retina as a relevant site to investigate brain synaptic transmission dysfunctions. J Psychiatr Res. 2018 May 1;103:75-82. (IF: 4.18)

Cosker E, **Schwitzer T**, Ramoz N, Ligier F, Lalanne L, Gorwood P, Schwan R, Laprévote V. The effect of interactions between genetics and cannabis use on neurocognition. A review. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Mar 2;82:95-106. (IF: 4.18)

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Bernardin F, Schwan R, Lalanne L, Ligier F, Angioi-Duprez K, **Schwitzer T**, Laprevote V. The role of the retina in visual hallucinations: A review of the literature and implications for psychosis. Neuropsychologia. 2017 Mar 2;99:128-138. (IF: 3.19)

Laprevote V, Heitz U, Di Patrizio P, Studerus E, Ligier F, **Schwitzer T**, Schwan R, Riecher-Rössler A. Why and how to treat psychosis earlier? Presse Med. 2016 Nov;45(11):992-1000. (IF: 1.07)

Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Laprevote V, 2016. The endocannabinoid system in the retina: from physiology to practical and therapeutic applications. Neural Plast. 2016;2016:1-10. (IF 3.6)

Schwitzer T, Robert MP, Giersch A, Angioi-Duprez K, Ingster-Moati I, Pon-Monnier A, Schwan R, Laprevote V. Transient Retinal Dysfunctions after Acute Cannabis Use.Eur Addict Res. 2016;22(6):287-291.(IF: 2.36)

Faure C, **Schwitzer T**, Hansen C, Randhawa S, 2016. Diagnostic and Therapeutic Challenges. Retina Phila. Pa. (IF 3.24)

Schwitzer T, Schwan R, Bernardin F, Jeantet C, Angioi-Duprez K, Laprevote V. 2016. Commentary: Anatomical constitution of sense organs as a marker of mental disorders. Front. Behav. Neurosci. 10, 56. (IF 3.27)

Schwitzer T, Gillet C, Bisch M, Di Patrizio P, Schwan R, Laprevote V. Consommations conjointes de cannabis et de tabac : connaissances cliniques et perspectives thérapeutiques. Therapie. 2016 Jun;71(3):315-322. (IF=0,78)

Laprevote V, **Schwitzer T**, Giersch A, Schwan R, 2015. Flash electroretinogram and addictive disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 56, 264. (IF 3.69)

Laprevote V, Schwan R, **Schwitzer T**, Rolland B., Thome J, 2015. Is there a place for off-label pharmacotherapy in cannabis use disorder? A review on efficacy and safety. Current Pharmaceutical design 21, 3298-305 (IF 3.45)

Schwitzer T, Schwan R, Angioi-Duprez K, Ingster-Moati I, Lalanne L, Giersch A, Laprevote V, 2015. The cannabinoid system and visual processing: A review on experimental findings and clinical presumptions. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 100–112. (IF 4.37)

Schwitzer T, Lavoie J, Giersch A, Schwan R, Laprevote V, 2015. The emerging field of retinal electrophysiological measurements in psychiatric research: a review of the findings and the perspectives in major depressive disorder. J. Psychiatr. Res. 70, 113-120. (IF 3.96)

Valorisation

1 brevet déposé le 28 février 2018 (FR 18/00175) sur un dispositif médical intégrant des mesures ophtalmologiques en santé mentale

Thomas Schwitzer 35%, Raymund Schwan 35%, Valérie Louis-Dorr 30%, Collaboration Ecole Polytechnique Paris, Incubateur X-UP

COMMUNICATIONS

Congrès internationaux

Communications orales avec résumé

Altered neuroretinal processing in regular cannabis users: an impact of cannabis on retinal neurotransmission? Schwitzer T. *12th Conference on cognitive neuropsychiatry, Neurex Network, Strasbourg, France, 28-29 mars 2017*

Disrupted retinal function in regular cannabis users. Schwitzer T. *11th Conference on cognitive neuropsychiatry, Neurex Network, Strasbourg, France, 29-31 mars 2016*

A non-human primate telemetry model for assessment of cardiac contractility parameters. Schwitzer T. *9th Annual Meeting of Safety Pharmacology Society (SPS) congress, Strasbourg, France, 15-18 Septembre, 2009*

Communications affichées avec résumé

Laprevote V, Bernardin B, Schwitzer T, Schwan R. Electroretinogram anomalies in schizophrenia patients with visual hallucinations. *6th Biennial Schizophrenia International Research Soociety Conference, Florence, 4-8 Avril 2018*

Bernardin F, Schwan R, Schwitzer T, Laprevote V. Retinal ganglion cells dysfunction in schizophrenia patients with visual hallucinations. *4th International Consortium meeting on Hallucination Research, Lille, 6th-8th November 2017*

Giersch A, Schwitzer T, Laprevote V, Franck N, Martin B, Lalanne L. Sense of time continuity and sequential effects at the ms level : patients with schizophrenia show the way. *16th Rhythm Production and Perception Workshop, Birmingham, UK, 3-5 July 2017*

Schwitzer T, Schwan R, Giersch A, Albuisson E, Angioi-Duprez K, Laprevote V. Neuroretinal dysfunctions in regular cannabis users: an impact of cannabis on retinal neurotransmission?. *25th European congress of Psychiatry (EPA), Florence, Italy, 1-4 April 2017*

Schwitzer T, Schwan R, Giersch A, Laprevote V. Retinal anomalies in schizophrenia patients and regular cannabis users: a potential way to a biological marker? *5th Biennial Schizophrenia International Research Society Conference (SIRS), Florence, Italia, 2-6 avril 2016*

Schwitzer T, Schwan R, Giersch A, Laprevote V. Alterations in retinal processing in regular cannabis users. *24th European congress of Psychiatry (EPA), Madrid, Spain, 12-15 mars 2016*

Schwitzer T, Schwan R, Giersch A, Laprevote V. The retinal pathways as a model to understand brain damages in cannabis users. *28th European congress of NeuroPsychoPharmacology (ECNP), Amsterdam, The Netherlands, 29-1 septembre 2015.*

Schwitzer T, Loriot S, Bétat A-M, Froget G, Forster R, Simonnard A. Validation of a non-human primate telemetry model for assessment of cardiac contractility parameters. *9th Annual Meeting of Safety Pharmacology Society (SPS) congress, Strasbourg, France, 15-18 Septembre, 2009.*

Schwitzer T, Bétat A-M, Froget G, Simonnard A, Forster R. Evaluation of cardiac contractility by left ventricular pressure measurement in telemetered Beagle dogs. *9th Annual Meeting of Safety Pharmacology Society (SPS) congress, Strasbourg, France, 15-18 Septembre, 2009.*

Jacquot V, Schwitzer T, Bétat A-M, Forster R, Froget G. Influence of circadian cycle on cardiovascular parameters in monkeys, dogs and minipigs. *9th Annual Meeting of Safety Pharmacology Society (SPS) congress, Strasbourg, France, 15-18 Septembre, 2009.*

Congrès nationaux

Communications orales avec résumé

Association between regular cannabis use and ganglion cell dysfunction. Schwitzer T. *9ème Congrès Français de Psychiatrie, Lyon, 29 Novembre-2 Décembre 2017*

Anomalies fonctionnelles rétiniennes chez les usagers réguliers de cannabis : vers des marqueurs potentiels de neurotransmission cérébrale ? Schwitzer T. *11e Congrès International de l'Albatros, Paris, 31 mai-2 Juin 2017*

Troubles de l'exploration visuelle dans la schizophrénie : synthèse et pistes de réflexions. Schwitzer T. *8ème Congrès Français de Psychiatrie, Montpellier, 23-26 novembre 2016*

Communications affichées avec résumé

Laprevote V, Schwitzer T, Schwan R. Augmentation de la complexité du signal EEG chez les usagers dépendants au cannabis. *16ème Congrès de l'encéphale, Paris, 24-26 janvier 2018*

Schwitzer T, Schwan R, Giersch A, Albuisson E, Angioi-Duprez K, Laprevote V. La rétine, une fenêtre du cerveau ? Dysfonctions neurorétiniennes chez les usagers réguliers de cannabis. *15ème Congrès de l'encéphale, Paris, 18-20 janvier 2017*

Laprevote V, Schwitzer T, Jeantet C, Caharel S, Lighezzolo-Alnot J, Schwan R. Impact de l'usage régulier de cannabis sur la fonction visuelle : de la rétine au cortex. *15ème Congrès de l'encéphale, Paris, 18-20 janvier 2017*

Schwitzer T, Schwan R, Giersch A, Laprevote V. Spectaculaires dysfonctions rétiniennes chez les usagers réguliers de cannabis. *10e Congrès International de l'Albatros, Paris, 1-3 Juin 2016*

Laprevote V, Schwitzer T, Albuisson E, Angioi-Duprez K, Schwan R. Impact des consommations régulières de cannabis sur la fonction visuelle précoce. *14ème Congrès de l'encéphale, Paris, 20-22 janvier 2016*

Rigon M, Schwitzer T, Angioi-Duprez K, Schwan R, Laprevote V. Étude électrophysiologique du fonctionnement rétinien dans la schizophrénie. *14ème Congrès de l'encéphale, Paris, 20-22 janvier 2016*

Schwitzer T, Giersch A, Schwan R, Angioi K, Ingster-Moati I, Laprevote V. Anomalies de la fonction rétinienne chez les usagers réguliers de cannabis. *13ème Congrès de l'encéphale, Paris, 20-23 janvier 2015*

Laprevote V, Schwitzer T, Schwan R. Toxicité cérébrale de l'usage régulier de cannabis : intérêt de l'étude du système visuel. *13ème Congrès de l'encéphale, Paris, 20-23 janvier 2015*

Laprevote V, Schwitzer T, Hingray C, Schwan R. Déterminants biologiques du syndrome de sevrage du cannabis mesurés chez un patient en hémodialyse. *13ème Congrès de l'encéphale, Paris, 20-23 janvier 2015*

Schwitzer T, Ingster-Moati I, Angioi K, Giersch A, Schwan R, Laprevote V. Impaired retinal processing in regular cannabis users: potential benefit of electroretinogram as a biomarker. *6ème Congrès Français de Psychiatrie, Nantes, 26-29 novembre 2014,*

Schwitzer T, Angioi K, Ingster-Moati I, Giersch A, Schwan R, Laprevote V. L'électrorétinogramme comme un possible marqueur des dysfonctions rétiniennes chez les usagers de cannabis. *8ème Congrès International de l'Albatros, Paris, France, 5-6 juin 2014*

TRAVAUX PEDAGOGIQUES

Chapitres de livres

Schwan R, Schwitzer T, Laprevote V. Prise en charge des patients présentant un trouble de l'usage de l'alcool aux urgences. Traité d'addictologie. Paris : Médecine-Sciences, Flammarion. 2016

Articles didactiques

Schwitzer T. Service sanitaire-Addictologie. 2018

Schwitzer T. La luminothérapie. La réponse du Psy. 2017

MEMBRE DE COMITES DE LECTURE DE REVUES

Analyses d'articles pour des journaux internationaux :

Schizophrenia Research (IF: 4,45)
The World Journal of Biological Psychiatry (IF: 4,16)
Journal of Abnormal Psychology (IF: 4,13)
Psychiatry Research (IF: 2,53)
Frontiers in Psychology (IF: 2.1)
Phytotherapy Research (IF: 2,69)
HSOA journal of ophthtalmology & clinical research

FONCTIONS D'INTERET GENERAL (activités adm.et responsabilités collectives)

Membre de commissions, comités, réseaux (distinguer participation et animation) etc

Membre du comité BASE (Bienveillance Accompagnement et Suivi des étudiants) pour l'accompagnement des étudiants en difficulté depuis 2018
Membre du réseau lorrain IT-neuro, rassemblant toutes les équipes lorraines de recherches en Neurosciences depuis 2017
Membre de la confédération francophone d'hypnose et de thérapies brèves (CFHTB) depuis 2012

2

ACTIVITES PEDAGOGIQUES

Enseignements

Enseignant au Module de Psychiatrie, UE 8, FGSM2, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2017 jusqu'à présent

Enseignant au Module de Psychiatrie, UE 4, FASM1, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2017 jusqu'à présent

Enseignant au Module de Psychiatrie, UE 6, FGSM3, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2018 jusqu'à présent

Enseignant au Séminaire de « Méthodologie de la Recherche en Psychiatrie », DES de Psychiatrie, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2016 jusqu'à présent

Coordinateur et Enseignant au séminaire de « Physiologie et stratégies thérapeutiques dans la dépression unipolaire », DES de Psychiatrie, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2017 jusqu'à présent

Enseignant au Séminaire de « Sémiologie psychiatrique et psychopharmacologie», DES de Psychiatrie, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2017 jusqu'à présent

Coordinateur et Enseignant au séminaire d' « Addictologie », DES de Psychiatrie, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2017 jusqu'à présent

Enseignant au Module de Psychiatrie, UE 2.6, 3ème année, IFSI Nancy Brabois, de 2011 à 2017

Enseignant au Module de Psychiatrie, UE 2.2.1, 1ère année, Ecole d'orthophonie, Faculté de Médecine de Nancy (Université de Lorraine), depuis 2018 jusqu'à présent

Jurys

Jury de M2 d'orthophonie, Faculté de Médecine de Nancy, Université de Lorraine

Lucine RICQ

Jury de M1, Université de Lorraine

Eloïse Finiels
Yanis Menzer
Alice Lucas
Ludovic Polli
Guiné Jean-Baptiste
Xenia Gordon
Marianne Menigoz
Florian Wencker
Laura Malbos

Jury de thèse d'exercice en Médecine :

Audrey Thirion, Faculté de Médecine de Nancy (Université de Lorraine), 2018
Alice Lucas, Faculté de Médecine de Nancy (Université de Lorraine), 2018

Missions pédagogiques

Tuteur pédagogique et Enseignant référent dans le cadre du service sanitaire

Tuteur pédagogique dans le cadre du comité BASE (Bienveillance Accompagnement et Suivi des étudiants)

3

ACTIVITES CLINIQUES

ACTIVITES DE SOINS

Responsabilité dans un service hospitalier

11.2016 - Présent	Chef de Clinique des Universités – Assistant des Hôpitaux Responsable d'une unité d'hospitalisation sous contrainte (SDT, SPI) et libre, en psychiatrie générale (22 lits) Pôle hospitalo-Universitaire de Psychiatrie du Grand Nancy (PHUGN) Pr Raymund Schwan

Activités de consultation

11.2016 - Présent	Consultations troubles de l'humeur résistants au CPN Consultations de Psychiatrie générale

4

ACTIVITES DE RECHERCHE

Un des défis actuels de la recherche en neurosciences et en psychiatrie est de pouvoir étudier le fonctionnement cérébral de manière indirecte en raison du difficile accès direct au fonctionnement du cerveau. Les enjeux de ces recherches sont l'identification de site appartenant au système nerveux central, partageant des propriétés similaires et pouvant fournir des indicateurs objectifs du fonctionnement cérébral. Le rôle de ces indicateurs pourrait être notamment l'étude de la physiopathologie sous tendant les troubles psychiatriques et addictifs et notamment les anomalies de neurotransmission. Parmi ces approches, la fonction rétinienne présente un intérêt particulier pour étudier de manière indirecte le fonctionnement du cerveau. La rétine est le premier stade du traitement de l'information visuelle et est une extension anatomique et développementale du système nerveux central. Elle est facile d'accès et sa fonction peut être étudiée avec des méthodes électro physiologiques qui sont standardisées, assurant ainsi la reproductibilité des résultats. Ces dernières années, plusieurs équipes ont évalué la fonction rétinienne avec ces techniques chez les patients souffrant de maladies mentales et des résultats intéressants ont pu être mis en évidence.

Les recherches que j'ai pu mener au sein de l'EA 7298 (UL) puis de l'INSERM U1114 se sont concentrées initialement sur l'utilisation de ces mesures chez les usagers de cannabis. Ensuite, j'ai souhaité élargir l'utilisation de ces techniques dans le champ large des troubles psychiatriques et addictifs, notamment le trouble dépressif majeur, la schizophrénie, l'utilisation d'alcool et de tabac pour lesquels de nouvelles recherches sont engagées, parallèlement à la poursuite de celles dans l'usage de cannabis. A partir ce ces mesures, nous souhaitons ainsi pouvoir dégager des indicateurs permettant d'orienter le clinicien vers des hypothèses pathologiques spécifiques ou d'évaluation de la réponse aux traitements. Pour cela, nous avons conçu un dispositif portatif en cours de développement intégrant des mesures rétiniennes et pouvant être facilement utilisable dans le champ des troubles psychiatriques et addictifs (partie Projet). Enfin, afin de valider les hypothèses physiopathologiques sous-jacentes à ces mesures, nous avons imaginé un programme de recherche plus large et incluant des mesures électro physiologiques, moléculaires, histopathologiques et génétiques (partie projet).

I. BILAN DES TRAVAUX DE RECHERCHE

1. Rétine et système cannabinoïde

Chez l'homme, la rétine est dotée d'un système cannabinoïde fonctionnel, ce qui implique que les exocannabinoïdes présents dans le cannabis consommé peuvent affecter le fonctionnement de la rétine (Schwitzer et al., 2016b, 2015b; Yazulla, 2008a). Les récepteurs cannabinoïdes CB1 et CB2 sont détectés dans la rétine humaine (Porcella et al., 2000; A. J. Straiker et al., 1999; Wei et al., 2009). Les récepteurs CB1 sont exprimés dans les segments extérieurs des photorécepteurs, la couche plexiforme interne, la couche plexiforme externe, la couche nucléaire interne, la couche des cellules ganglionnaires et l'épithélium pigmentaire rétinien. Les récepteurs CB2 sont exprimés dans les cellules de l'épithélium pigmentaire rétinien humain. Les deux principaux ligands endocannabinoïdes -2-Arachidonoylglycerol (2-AG) et Anandamide sont également détectés dans la rétine humaine (Chen et al., 2005; Matias et al., 2006; Stamer et al., 2001). Des taux élevés de 2-AG sont présents dans la rétine, tandis que l'anandamide est exprimé à un niveau inférieur. Plusieurs enzymes sont impliquées dans la régulation du niveau cellulaire des endocannabinoïdes rétiniens et permettent la dégradation des ligands cannabinoïdes: hydrolase d'amide d'acides gras (FAAH), monoacylglycérol lipase (MGL) et cyclooxygénase-2 (COX-2) (Wang et al. , 2011; Wei et al., 2009). La FAAH est une protéine membranaire intégrale qui est exprimée dans la rétine humaine, en particulier dans l'épithélium pigmentaire rétinien (Wei et al., 2009). Des découvertes récentes font également état d'une détection de COX-2 dans la rétine humaine (Wang et al., 2011).

Le rôle du système endocannabinoïde dans la régulation de la neurotransmission dans la rétine est bien décrit chez les espèces animales (Schwitzer et al., 2015b; Yazulla, 2008b). Les agonistes des cannabinoïdes sont impliqués dans les modulations réversibles et dose-dépendantes des courants de calcium, de potassium et de chlore dans les cellules bipolaires, les bâtonnets, les cônes et les cellules ganglionnaires (Fan et Yazulla, 2003, 2004, 2005, 2007; Lalonde et al., 2006; Opere et al., 2006; A. Straiker et al., 1999; Straiker et Sullivan, 2003; Yazulla et al., 2000;

Zhang et al., 2013). Étant donné que les canaux ioniques internes et externes jouent un rôle majeur dans la neurotransmission rétinienne, nous supposons un impact des exocannabinoïdes présents dans le cannabis sur la neurotransmission rétinienne chez l'homme (Laprevote et al., 2015). Un effet direct des cannabinoïdes sur l'activité enzymatique et la libération de neurotransmetteurs a également été décrit dans la rétine d'espèces animales (Gawienowski et al., 1982; Middleton et Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Warrier et Wilson, 2007; Weber et Schlicker, 2001). Dans la rétine bovine, le THC induit une modulation dose-dépendante de l'activité de la monoamine oxydase (Gawienowski et al., 1982). Dans la rétine bovine isolée, les agonistes des récepteurs CB1 inhibent la libération d'aspartate, qui est bloquée par les antagonistes des cannabinoïdes (Opere et al., 2006). Dans les rétines perfusées de cobayes, la libération de la dopamine et de la noradrénaline est inhibée par l'activation des récepteurs CB1, qui elle-même est bloquée par les antagonistes des cannabinoïdes (Schlicker et al., 1996; Weber et Schlicker, 2001). Fait intéressant, la libération de dopamine mais également de GABA et de glutamate peut être modulée par les cannabinoïdes (Middleton et Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Straiker et Sullivan, 2003; Warrier et Wilson, 2007; Weber et Schlicker, 2001). Le système endocannabinoïde rétinien est également impliqué dans d'autres mécanismes neuronaux physiologiques tels que la plasticité neuronale et la neuroprotection (Schwitzer et al., 2016b).

Publications

Schwitzer T, Schwan R, Angioi-Duprez K, Ingster-Moati I, Lalanne L, Giersch A, Laprevote V, 2015.
The cannabinoid system and visual processing: A review on experimental findings and clinical presumptions.
Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 100–112.

Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Laprevote V, 2016.
The endocannabinoid system in the retina: from physiology to practical and therapeutic applications.
Neural Plast. 2016;2016:1-10.

2. Anomalies fonctionnelles rétiniennes chez les usagers réguliers de cannabis

La consommation régulière de cannabis est un enjeu de santé publique, car le cannabis est une drogue pouvant entraîner une dépendance et l'une des plus utilisées dans les pays industrialisés (Degenhardt et al., 2008). Le cannabis est connu pour agir sur plusieurs voies de neurotransmission cérébrale notamment glutamatergique et GABAergique (Bossong et Niesink, 2010). Cependant, il est difficile d'accéder directement au cerveau en fonctionnement et de déterminer la modulation à long terme des différentes voies de neurotransmission induite par des consommations régulières de cannabis. Des mesures indirectes sont donc nécessaires.

Le fonctionnement des neurones rétiniens peut être évalué objectivement à l'aide de l'électrorétinogramme (ERG) (Holder et al., 2010). L'ERG enregistre le potentiel électrique provenant des différentes couches de neurones rétiniens en réponse à différents types de stimulations lumineuses (Holder et al., 2010). La réponse rétinienne enregistrée est associée aux changements de niveaux de neurotransmetteurs à travers la rétine (Hoon et al., 2014). À l'aide d'un flash lumineux généralement de couleur blanche, le flash ERG (fERG) évalue le fonctionnement des photorécepteurs –cônes et bâtonnets- et des cellules bipolaires en lien avec ces photorécepteurs (McCulloch et al., 2015). En utilisant des renversements de damiers noirs et blancs, le pattern ERG (PERG) évalue la fonction des cellules ganglionnaires (Bach et al., 2013; Porciatti, 2015). Des protocoles standardisés sont disponibles afin d'assurer des résultats reproductibles (Bach et al., 2013; McCulloch et al., 2015).

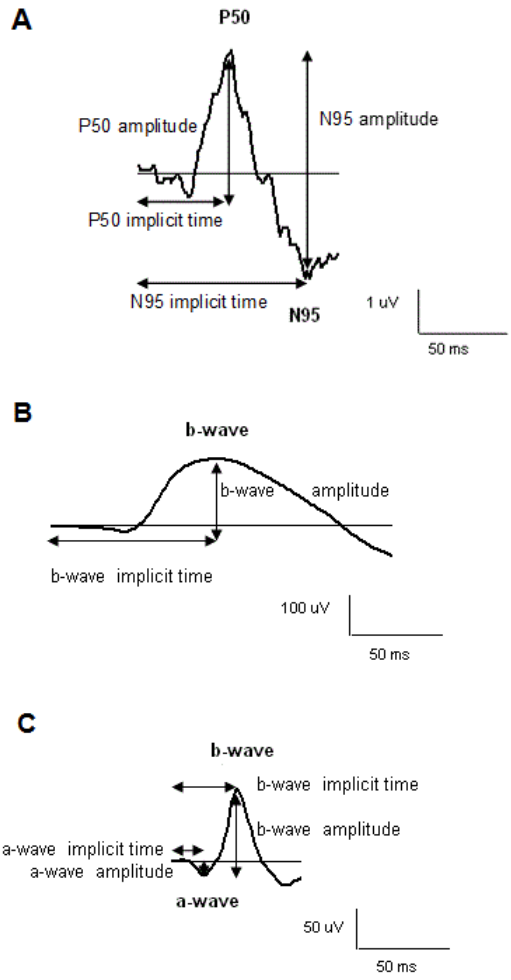


Figure 1 : Tracés typiques d'électrorétinogramme pattern (PERG) mesurant la réponse électrophysiologique des cellules ganglionnaires (A), d'ERG flash mesuré en condition scotopique et évaluant le fonctionnement du système des bâtonnets (B) et d'ERG flash obtenu en condition photopique et mesurant le fonctionnement du système des cônes (C). Les flèches montrent comment les paramètres sont mesurés : le temps de culmination et l'amplitude des ondes P50, N95 pour le PERG, et des ondes a- et b pour l'ERG flash

ETAGE DES CELULLES GANGLIONNAIRES

La première étude que nous avons menée visait à évaluer l'étage des cellules ganglionnaires de la rétine (RGC) car il nous paraissait particulièrement pertinent pour étudier l'impact des consommations régulières de cannabis sur la transmission synaptique chez l'homme, et ce pour les raisons suivantes. Le stade des RGC est le dernier stade et le plus intégré du traitement de l'information visuelle au niveau rétinien. Il est le premier stade de la rétine fournissant des informations visuelles sous la forme de potentiels d'action tels que ceux trouvés dans le cerveau (Hoon et al., 2014). Le système endocannabinoïde est détecté dans les RGC et participe à la régulation de la transmission synaptique des RGC (Yazulla 2008). Par exemple, chez les rongeurs, les agonistes des cannabinoïdes réduisent la libération de glutamate au niveau des RGC. Chez l'homme, le glutamate est également un important transmetteur impliqué dans la physiologie rétinienne et dans la transmission verticale des informations visuelles rétiniennes. L'action du cannabis sur la transmission glutamatergique centrale pourrait donc perturber le fonctionnement des RGC chez l'homme. Pour vérifier cette hypothèse, nous avons utilisé le PERG. Le PERG permet de calculer la moyenne d'un nombre élevé de réponses, garantissant ainsi la reproductibilité des résultats. En utilisant le PERG, le meilleur marqueur de la fonction des RGC est une onde négative, l'onde N95, dont deux paramètres sont généralement issus et nommés l'amplitude et le temps de culmination (qui désigne le temps nécessaire pour atteindre l'amplitude maximale de l'onde N95). Étant donné le rôle du système cannabinoïde dans la régulation de la transmission synaptique des RGC, nous avons émis l'hypothèse que la réponse des RGC pouvait être affectée par une consommation régulière de cannabis.

Cette étude a été menée chez 28 consommateurs réguliers de cannabis et 24 sujets contrôles appariés en âge et en sexe. Avant de participer à l'étude, les volontaires ont fourni leurs antécédents médicaux et de consommation de substances détaillés, ont subi une évaluation psychiatrique complète et signé des formulaires de consentement détaillant tous les aspects de la recherche. Le protocole d'étude répondait aux exigences de la déclaration d'Helsinki et avait été approuvé par le comité d'éthique du Centre Hospitalier Régional Universitaire de Nancy (CHRU).

Cette étude fait partie d'un projet plus important, Causa Map, qui étudie l'impact de la consommation régulière de cannabis sur le système visuel. Tous les participants ont également subi des évaluations neuropsychologiques et des enregistrements EEG au cours de plusieurs tâches visuelles. Compte tenu du caractère novateur de ces mesures, le protocole fournit une analyse intermédiaire, présentée ici, axée sur le fonctionnement des cellules ganglionnaires de la rétine.

Les critères d'inclusion pour le groupe cannabis étaient la consommation régulière de cannabis au moins 7 fois par semaine au cours du dernier mois, un dépistage positif de la toxicologie urinaire pour les métabolites du tétrahydrocannabinol (THC), aucune autre consommation de substance illicite au cours du dernier mois, un dépistage négatif de la toxicologie urinaire pour d'autres substances illicites, et l'absence de diagnostic du DSM-IV pour les troubles de l'Axe I. Étant donné que le tabac est régulièrement mélangé avec du cannabis dans les joints, les utilisateurs de cannabis pouvaient répondre aux critères de dépendance au tabac selon le test de Fagerström. Les consommateurs de cannabis étaient tenus de présenter au moins 12 heures d'abstinence de la consommation de cannabis afin d'éviter tout dysfonctionnement cognitif dû à la consommation aigu de cannabis. Les critères d'inclusion pour les sujets témoins sains étaient l'absence d'antécédents de consommation de substances illicites, un test de toxicologie urinaire négatif pour les métabolites du THC et d'autres drogues illicites testées, et aucun antécédent de diagnostic du DSM-IV de troubles psychiatriques de l'axe I. Tous les participants étaient âgés de 18 à 35 ans, n'avaient pas d'antécédent de maladie neurologique, pas d'antécédent familial de schizophrénie ou de trouble bipolaire, et ne prenaient pas de médication, à l'exception des contraceptifs oraux chez les femmes. Ils n'avaient pas d'antécédent de maladie ophtalmologique, à l'exception des troubles de réfraction corrigés. L'acuité visuelle mesurée avec l'échelle de Monoyer était d'au moins 10/10 dans chaque œil pour tous les participants. Aucun des participants n'a signalé de symptômes visuels. Si les participants présentaient une dépendance à l'alcool en fonction de leur score d'AUDIT, ils étaient exclus de l'étude. L'échelle M.I.N.I. a été administrée pour évaluer les antécédents de maladies psychiatriques et d'usage de substances psychoactives. En outre, le test de dépistage de l'abus de cannabis (CAST), le test de Fagerström et l'AUDIT ont été réalisés pour évaluer la

consommation, l'abus ou la dépendance à l'égard du cannabis, du tabac et de l'alcool, respectivement.

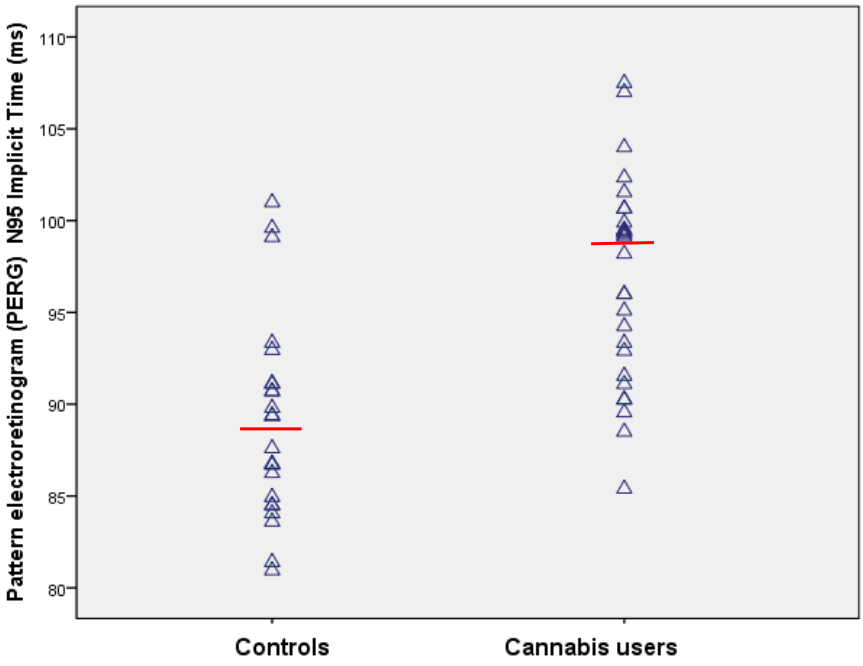
L'importance de la consommation de cannabis a fait l'objet d'une évaluation clinique lors d'un entretien et d'un questionnaire comme suit: âge du début de la consommation régulière de cannabis, nombre total d'usages de cannabis, nombre moyen de joints fumés quotidiennement et hebdomadairement au cours du dernier mois, nombre moyen de grammes fumés chaque semaine. Afin d'obtenir une confirmation objective de la consommation de cannabis, des tests de dépistage urinaire pour le cannabis, la buprénorphine, les benzodiazépines, la cocaïne, les opiacés ont été réalisés immédiatement avant le test d'ERG.

Le PERG a été enregistré selon les recommandations de la Société Internationale pour l'électrophysiologie clinique de la vision (ISCEV) 21. Le système MonPackOne (Metrovision, Perenchies, France) a été utilisé pour la stimulation, l'enregistrement et l'analyse. Les signaux électriques ont été enregistrés simultanément à partir des deux yeux (moyennés pour d'analyse), sur des pupilles non dilatées, avec des électrodes DTL (Dawson, Trick & Litzkow, Metrovision, Perenchies, France) placées dans le cul de sac conjonctival. Des électrodes de masse et de référence ont été fixées au front et au niveau des canthi externes. Un renversement de damiers noir et blanc a été utilisé, avec une taille de 0,8 °, un niveau de contraste de 93,3%, une ambiance lumineuse blanche à 100 candela / m² à luminance constante et une vitesse de stimulation de 4 renversements par seconde. Le sujet était placé à un mètre de l'écran. Dans le cas de sujets présentant des troubles de la réfraction, une correction optique appropriée a été fournie. Au moins 220 réponses ont été enregistrées pour chaque participant pour obtenir le meilleur rapport signal / bruit. Les données PERG ont été analysées avec Moniteur Ophtalmique (Metro Vision, Perenchies, France). Deux composants principaux sont généralement décrits sur un tracé typique de PERG: un composant électropositif, P50, suivi d'un composant électronégatif, N95. N95 est attribué aux cellules ganglionnaires de la rétine et reflète leur réponse. La P50 reflète la réponse des cellules ganglionnaires de la rétine et des photorécepteurs maculaires et sert à évaluer la fonction maculaire. Deux paramètres principaux sont dérivés de P50 et N95, connus par convention comme

l'amplitude mesurée en microvolts (µV) et le temps de culmination (c'est-à-dire la latence) mesuré en millisecondes (ms). L'amplitude de N95 est mesurée du creux du N95 au sommet du P50. L'amplitude de P50 est mesurée du creux de l'inconstante onde N35 - ou de la ligne de base - au sommet de la P50. Le temps de culmination désigne le temps nécessaire pour atteindre les amplitudes maximales des ondes N95 et P50.

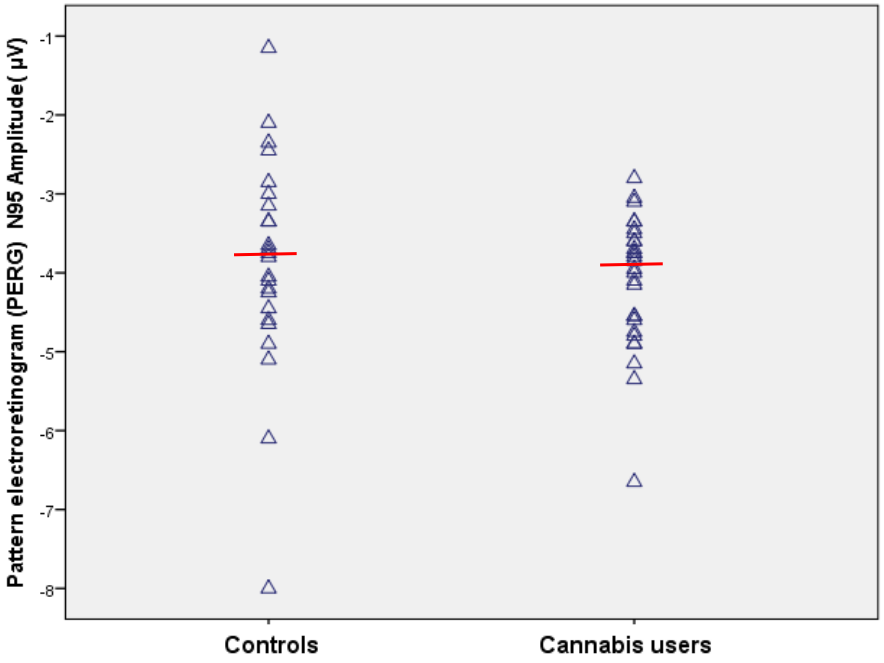
Les résultats indiquent que les consommateurs réguliers de cannabis semblent afficher une augmentation du temps de culmination de l'onde N95 du PERG sans aucune modification de l'amplitude. Ces résultats sont en faveur d'un retard d'environ 10 ms dans la transmission des potentiels d'action évoqués par les RGC et sont indépendants de l'effet de l'alcool.

Figure 2: Représentation graphique par groupes de points du temps de culmination de l'onde N95 du PERG pour les usagers réguliers de cannabis et les sujets sains avec les médianes



Légende: Contrôles: n=24; médiane: 88.48ms [95% CI; 85.0:91.1]. Usagers de cannabis: n=28; médiane: 98.65ms [95% CI; 93.4:99.5]. (*P* = 0.0001: Mann-Whitney U test).

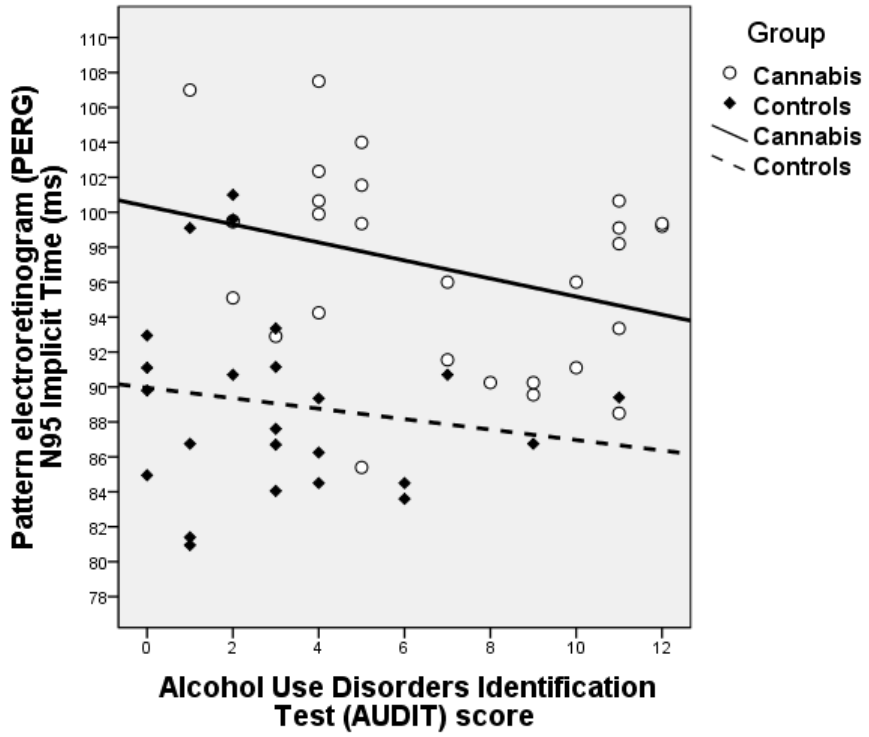
Figure 3: Représentation graphique par groupes de points de l'amplitude de l'onde N95 du PERG pour les usagers réguliers de cannabis et les sujets sains avec les médianes



Légende:

Contrôles: n=24; médiane: -3.78 µV [95% CI; -4.45:-3.15]. Usagers de cannabis: n=28; médiane: -3, 90 µV [95% CI; -4.55:-3.60] (P=0.368: Mann-Whitney U test).

Figure 4: Investigation graphique de l'interaction entre le temps de culmination de l'onde N95 du PERG et le score d'AUDIT



Légende: Lignes de régression linéaire du temps de culmination de N95 sur le score d'AUDIT pour les contrôles et les usagers de cannabis. Les intervalles de confiance à 95% des deux pentes négatives se chevauchent et les lignes ne se croisent pas entre les plages des valeurs observées (témoins: -0,299; [-1,114; 0,516]; cannabis: -0,517; [-1,111; 0,078]).

Publication

Schwitzer T, Schwan R, Albuisson E, Giersch A, Lalanne L, Angioi-Duprez K, Laprevote V. Association Between Regular Cannabis Use and Ganglion Cell Dysfunction. JAMA Ophthalmol. 2017 Jan 1;135(1):54-60.

ÉTUDE DE L'IMPACT DES GENES CNR1, CNR2 ET COMT SUR LE FONCTIONNEMENT DU SYSTEME RETINIEN CHEZ LES USAGERS REGULIERS DE CANNABIS

Encadrement et publication

Encadrement :
Eve Cosker (Master 2 de Biologie Intégrative et Physiologie, Université Paris VI)

Publication :
Cosker E, Schwitzer T, Ramoz N, Ligier F, Lalanne L, Gorwood P, Schwan R, Laprévote V. The effect of interactions between genetics and cannabis use on neurocognition. A review. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Mar 2;82:95-106.

Étant donné que des variations génétiques influencent les effets du cannabis sur la cognition, nous nous sommes demandé s'il existe des déterminants biologiques susceptibles de faire varier le fonctionnement rétinien chez les usagers réguliers de cannabis. Le but de cette étude était d'explorer l'hypothèse d'un effet du polymorphisme des gènes *CNR1, CNR2* ou *COMT* sur la latence de l'onde N95 en plus des effets du cannabis. Nous avons fait l'hypothèse d'une interaction entre les variations génétiques et la consommation de cannabis chez les usagers réguliers de cannabis.

Un prélèvement salivaire était obtenu par salivation des participants à l'aide d'un kit de prélèvement Oragene® (DNA Genotek, Ottawa, Canada). L'analyse génétique était réalisée dans l'unité INSERM U894 à Paris. La purification manuelle de l'ADN était réalisée selon les indications du fabriquant (DNA Genotek, Ottawa, Canada).
La détermination du génotype des SNPs rs1049353, rs1535255, rs6454674, rs806379 de *CNR1*, rs2229579, rs2501432 de *CNR2*, et rs4680 de *COMT* était réalisée avec TaqMan® SNP genotyping assay. Le mélange de polymérisation (TaqMan® Universal PCR Master Mix) et la sonde spécifique du SNP (Single Nucleotide polymorphisme- le polymorphisme d'un seul nucléotide dans un gène) étaient préparés selon les indications du fabriquant et mis au contact de l'ADN

génomique. Une réaction de PCR était effectuée puis une analyse réalisée à l'aide de l'appareil de détection Opticon® (MJ research/Biorad) avec le logiciel Opticon2®.

Nos résultats ont montré un effet du SNP rs6454674 de CNR1. L'allèle G était associé à une latence de l'onde N95 augmentée chez les usagers de cannabis et les témoins par rapport à l'allèle T. Les porteurs de l'allèle G avaient une latence de l'onde N95 augmentée par rapport aux sujets TT. Il n'y avait pas d'interactions gène/groupe. Nous n'avons pas mis en évidence d'effets des autres SNPs de *CNR1* ni des gènes *CNR2* et *COMT*.

En conclusion, nos données indiquent un effet du SNP rs6454674 de *CNR1* sur la latence de l'onde N95 en plus de l'effet de la consommation de cannabis. Il s'agit de la première étude montrant un effet visuel de *CNR1*. Aussi ces résultats sont à considérer avec précaution. L'explication biologique d'une telle association reste par ailleurs à préciser. Il semble toutefois qu'il y ait un effet cumulatif entre les effets du cannabis et ceux de rs6454674.

STADE DES CELLULES GANGLIONNAIRES ET DES CELLULES BIPOLAIRES ET PHOTORECEPTRICES

L'étude suivante que nous avons menée avait un triple objectif : 1) confirmer les résultats tirés de l'analyse préliminaire sur le nombre total de patients prévu dans l'étude initiale, 2) évaluer si les stades rétiniens antérieurs étaient également modifiés chez les consommateurs réguliers de cannabis 3) évaluer la spécificité et la sensibilité des éventuelles anomalies fonctionnelles de la rétine.

Le but de cette étude était de vérifier si les premiers stades impliqués dans le traitement rétinien de l'information visuelle, en particulier les cellules bipolaires et photoréceptrices, étaient altérés chez les consommateurs réguliers de cannabis. Étant donné le rôle du système cannabinoïde dans la régulation de la libération de neurotransmetteurs dans les photorécepteurs rétiniens et les cellules bipolaires et ganglionnaires, nous avons émis l'hypothèse que des dysfonctionnements pourraient être observés chez les consommateurs réguliers de cannabis aux stades précoces et ultimes du traitement rétinien.

Cette étude a été réalisée chez 53 usagers réguliers de cannabis et 29 sujets sains selon les mêmes modalités de recrutement décrites précédemment. Dans cette étude, l'ERG flash et l'ERG pattern ont été enregistrés. Le protocole de l'ERG pattern est similaire à celui décrit précédemment. Les enregistrements d'ERG flash ont été effectués dans des conditions d'obscurité et de lumière. Les participants étaient placés à 30 centimètres de l'écran. Ils ont été adaptés à l'obscurité pendant une période de 20 minutes avant l'enregistrement de l'ERGf adapté à l'obscurité (appelé scotopique 0.01). Ils ont ensuite été adaptés à la lumière pendant 10 minutes à un fond clair réglé à 30 candela / m² (cd / m²) géré par le système MonPackONE avant la réalisation de la séquence du fERG adaptée à la lumière (appelé photopique 3.0). Au moins 8 et 16 réponses, pour les ERG flash adaptés à l'obscurité et à la lumière respectivement, ont été enregistrées pour chaque participant. Chaque réponse rétinienne est appelée en fonction de l'intensité lumineuse du flash exprimée en candela.m².s^{-1}. Pour évaluer le fonctionnement du système des bâtonnets et des

cônes séparément, des mesures d'ERG flash 0,01 adapté à l'obscurité et d'ERG flash 3,0 adapté à la lumière ont été effectuées.

Les données PERG et fERG ont été analysées avec Moniteur Ophtalmique (Metrovision, Pérenchies, France). Les deux composants principaux habituellement décrits sur un tracé typique de fERG sont un composant électronégatif, onde a, suivi d'un composant électropositif, onde b. L'onde a n'est pas détectée dans la réponse fERG 0,01 adaptée à l'obscurité car elle est masquée par l'onde b. L'onde a est attribuée aux photorécepteurs rétiniens et l'onde b est attribuée aux cellules bipolaires rétiniennes, post-synaptiques aux photorécepteurs. Deux paramètres principaux sont dérivés des ondes a et b, connues par convention comme l'amplitude mesurée en microvolts (μV) et le temps de culmination mesuré en millisecondes (ms). L'amplitude de l'onde a est mesurée à partir de la ligne de base jusqu'au creux de l'onde a. L'amplitude de l'onde b est mesurée du creux de l'onde a au sommet de l'onde b. Le temps de culmination désigne le temps nécessaire pour atteindre les amplitudes maximales des ondes a et b.

Dans cette étude, nous avons constaté un retard du traitement rétinien de l'information chez les consommateurs réguliers de cannabis par rapport aux témoins à deux stades critiques, à savoir les cellules bipolaires et ganglionnaires. Ces résultats suggèrent un retard d'environ 6 ms dans l'émission des potentiels d'action par les cellules ganglionnaires de la rétine chez les consommateurs de cannabis, ce qui se traduit par une augmentation du temps de culmination de l'onde N95 au PERG. Un autre résultat de cette étude est le retard observé chez les consommateurs réguliers de cannabis dans la réponse des cellules bipolaires des cônes - un stade plus précoce du traitement dans la rétine - démontré par une augmentation du temps de culmination de l'onde b du fERG 3,0 adapté à la lumière. Ce résultat confirme un retard dans la variation progressive des potentiels de membrane dans les cellules bipolaires des cônes d'environ 0,5 à 1 ms chez les consommateurs de cannabis par rapport aux témoins. Aucune anomalie n'a été observée dans le fonctionnement des photorécepteurs ni dans les cellules bipolaires connectées aux bâtonnets. Les effets observés sont indépendants de l'effet de l'alcool.

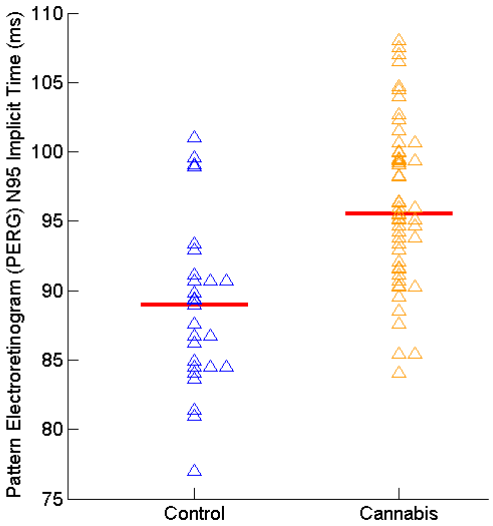


Figure 5. Diagramme à points du temps de culmination de l'onde N95 du PERG (ms) pour les utilisateurs de cannabis (n = 53) et les contrôles (n = 29) avec médiane. Les consommateurs de cannabis ont présenté une augmentation du temps de culmination et la différence entre les groupes est hautement significative (p = 0,0001; test U de Mann-Whitney).

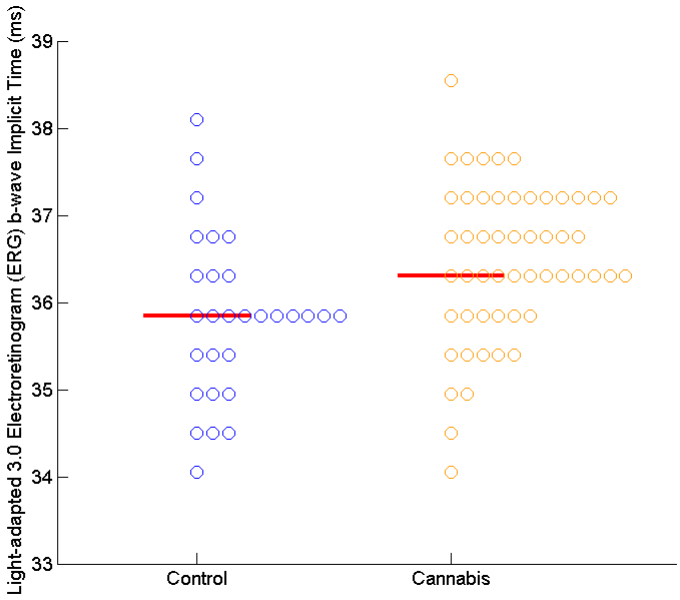
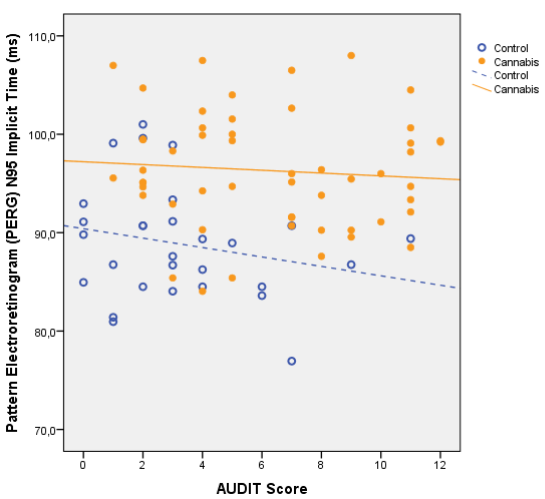


Figure 6. Diagramme à points du temps de culmination de l'onde b de l'ERG flash adapté à la lumière (ms) pour les utilisateurs de cannabis (n = 53) et les contrôles (n = 29) avec médiane. Les consommateurs de cannabis ont présenté une augmentation du temps de culmination et la différence entre les groupes est hautement significative (p = 0,002; test U de Mann-Whitney).



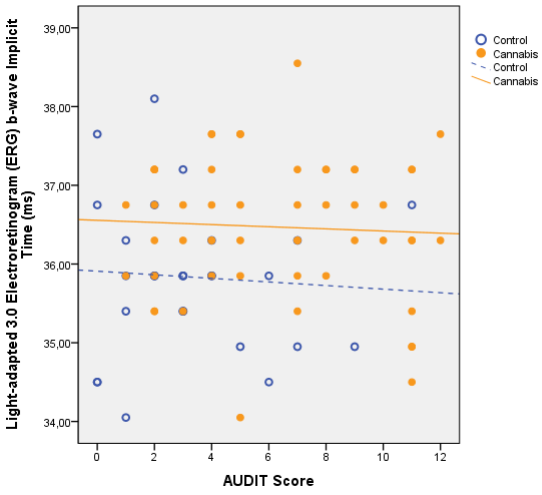


Figure 7 & 8: Investigation graphique de l'interaction entre le temps de culmination de l'onde N95 du PERG et de l'onde b de l'ERG flash série photopique 3.0 et le score d'AUDIT

Légende: Lignes de régression linéaire du temps de culmination de N95 et de l'onde b sur le score d'AUDIT pour les contrôles et les usagers de cannabis. Sur les deux graphe, les intervalles de confiance à 95% des deux pentes négatives se chevauchent et les lignes ne se croisent pas entre les plages des valeurs observées (contrôles: -0.479; [-1.285; 0.328]; usagers de cannabis: -0.144; [-0.625; 0.337]) et (contrôles: -0.023; [-0.158; 0.112]; usagers de cannabis: -0.014; [-0.087; 0.060]), respectivement pour l'onde N95 et l'onde b.

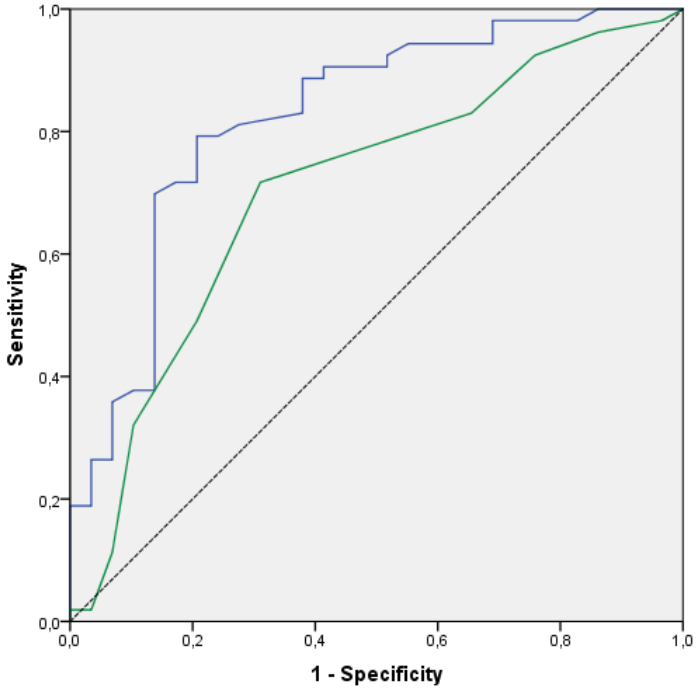


Figure 9. Courbes ROC. A) La courbe bleue est liée au temps de culmination de N95. AUC = 0,83; IC 95% [0,73; 0,92]; p = 0,0001 pour la valeur seuil de 91,3 ms (6 contrôles sur 29 se situent en dessous du seuil, avec une spécificité estimée à 79,3% (IC à 95% [0,62; 0,90]) alors que 11 sur 53 consommateurs de cannabis réguliers sont au-dessus du seuil, avec une sensibilité estimée à 79,2% (IC à 95% [0,67; 0,88])). B) La courbe verte est liée au temps de culmination de l'onde b du fERG série photopique 3,0. AUC = 0,71; IC à 95% [0,58; 0,83]; p = 0,002 pour la valeur seuil de 36,1 ms (20 contrôles sur 29 se situent en dessous du seuil, avec une spécificité estimée à 69% (IC à 95% [0,51; 0,83]), alors que 38 sur 53 utilisateurs de cannabis se situent au-dessus du seuil, avec une sensibilité estimée à 71,7% (IC à 95% [0,58; 0,82]).

Publication

Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Lalanne L, Albuisson E, Laprevote V. Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: The retina as a relevant site to investigate brain synaptic transmission dysfunctions. J Psychiatr Res. 2018 May 1;103:75-82.

LOCALISATION SPATIALE DES ANOMALIES RETINIENNES

Encadrement et publication

Encadrement :
Marie-Laure Henrion et Daphné Sarre (thèse de médecine, DES de Psychiatrie)

Publication :

Schwitzer T, Henrion ML, Sarre D, Albuisson E, Angioi-Duprez K, Giersch A, Lalanne L, Schwan R, Laprevote V. Spatial localization of retinal anomalies in regular cannabis users: the relevance of the multifocal electroretinogram. Schizophrenia Research. In press (IF: 3.96)

Les résultats précédemment observés ont été extraits du fERG et du PERG fournissant des informations sur les réponses globales de la rétine (Bach et al., 2013; McCulloch et al., 2015). En conséquence, ils ne peuvent pas fournir d'informations précises sur les zones rétiniennes locales qui pourraient être à l'origine de ces dysfonctionnements rétiniens. Afin d'évaluer les réponses rétiniennes locales susceptibles de nous renseigner sur la distribution spatiale de ces dysfonctionnements rétiniens, nous avons enregistré le mfERG dans l'échantillon d'utilisateurs de cannabis réguliers de notre précédente étude.

Le mfERG enregistre les propriétés spatiales de la fonction du système des cônes (Hood, 2000). Le stimulus est composé de plusieurs hexagones dont la taille augmente progressivement du centre vers la périphérie de l'écran (Holder et al., 2010). Chaque hexagone est illuminé de manière pseudo-aléatoire par une stimulation flash et informe sur une réponse locale du système des cônes. Les enregistrements mfERG permettent d'évaluer de multiples réponses locales dérivées de chaque hexagone. Trois ondes principales sont régulièrement décrites: N1, P1 et N2. N1 représente le premier composant électronégatif suivi d'une onde électropositive P1, elle-même suivie d'un composant électronégatif N2. Les amplitudes et les temps de culmination de chaque vague ont été évalués (Hood et al., 2012). N1 résulte de l'hyperpolarisation des cellules bipolaires OFF et P1 de la dépolarisation des cellules bipolaires ON. Il est probable que N1 partage partiellement l'origine avec l'onde a- du fERG enregistré dans des conditions

photopiques et les ondes P1 et N2 avec l'onde b- du fERG enregistré dans des conditions photopiques (Holder et al., 2010).

Le but de cette étude était d'évaluer les propriétés spatiales du système des cônes à l'aide de mesures de mfERG chez des consommateurs réguliers de cannabis par rapport aux témoins. Notre hypothèse était que les dysfonctionnements rétiniens précédemment observés chez les consommateurs réguliers de cannabis étaient dus à une distribution spatiale spécifique des altérations de la fonction rétinienne.

Les mesures du mfERG ont été enregistrées conformément aux recommandations de l'ISCEV (Hood et al., 2012). Le système MonPackONE (Metrovision, France) a été utilisé pour la stimulation, l'enregistrement et l'analyse. Les signaux électriques ont été enregistrés par des stimulations monoculaires, sur des pupilles dilatées (Tropicamide 0,5%) avec des électrodes de type Dawson-Trick-Litzkow (DTL, Metrovision, France) placées au fond du sac conjonctival. Les électrodes de masse et de référence étaient fixées au front et aux canthi externes.

La matrice de stimulation consistait en un écran de 61 éléments hexagonaux qui ont été modulés entre blanc et noir selon une séquence pseudo-aléatoire. La luminance de la stimulation était de 100 candela / m² (cd / m²). L'écran de stimulation était recouvert d'un fond uniformément éclairé avec une luminance réglée à 30 cd / m², généré par le système MonPackOne, afin d'éliminer la réponse des bâtonnets. La fréquence des stimuli a été réglée à 75 Hz. Les participants étaient placés à 30 centimètres de l'écran. Tous les sujets ont bénéficié d'une correction optique adaptée et ont été invités à fixer le fixateur rouge central sur l'écran. Toutes les réponses associées à des clignements des yeux ou des mouvements des yeux ont été rejetées. Au moins 5000 réponses ont été enregistrées pour chaque œil de chaque participant avec un niveau de bruit maintenu inférieur à 5 kiloohm (KΩ) pour obtenir le meilleur rapport signal / bruit.

Les données mfERG ont été analysées avec Monitor Ophthalmic (Metrovision, France). Les réponses mfERG ont été calculées en moyenne sur cinq régions rétiniennes: <2 degrés, 2-5 degrés, 5-10 degrés, 10-15 degrés et> 15 degrés.

Figure 17: Exemple d'un tracé typique d'une réponse obtenue avec l'ERG multifocal avec les principaux pics N1, P1 et N2

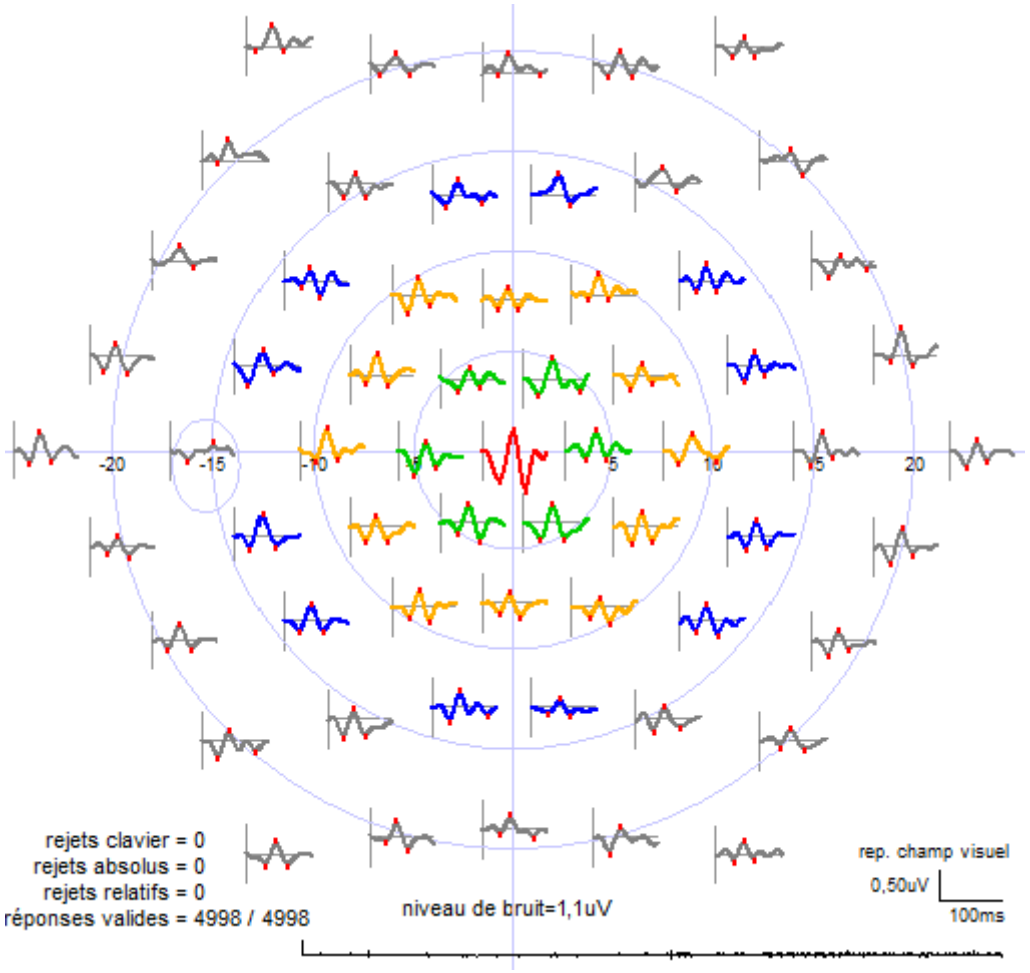


Figure 18: Exemple de tracé complet d'ERG multifocal réalisé avec des électrodes DTL

Les résultats montrent que chez les consommateurs réguliers de cannabis, il y a eu une augmentation significative des temps de culmination (+1 à 2 ms) pour N2 (<2 degrés), N2 et P1 (2-5 degrés), P1 et N1 (5-10 degrés), et P1 (10-15 degrés). Une diminution isolée de l'amplitude de N1 (2-5 degrés) a également été constatée. Cela indique qu'il y a un retard dans la transmission du signal par le système des cônes, principalement par les cellules bipolaires ON et OFF, et majoritairement dans la rétine centrale - la macula et la région maculaire - et à la périphérie proche, chez les consommateurs réguliers de cannabis par rapport aux contrôles.

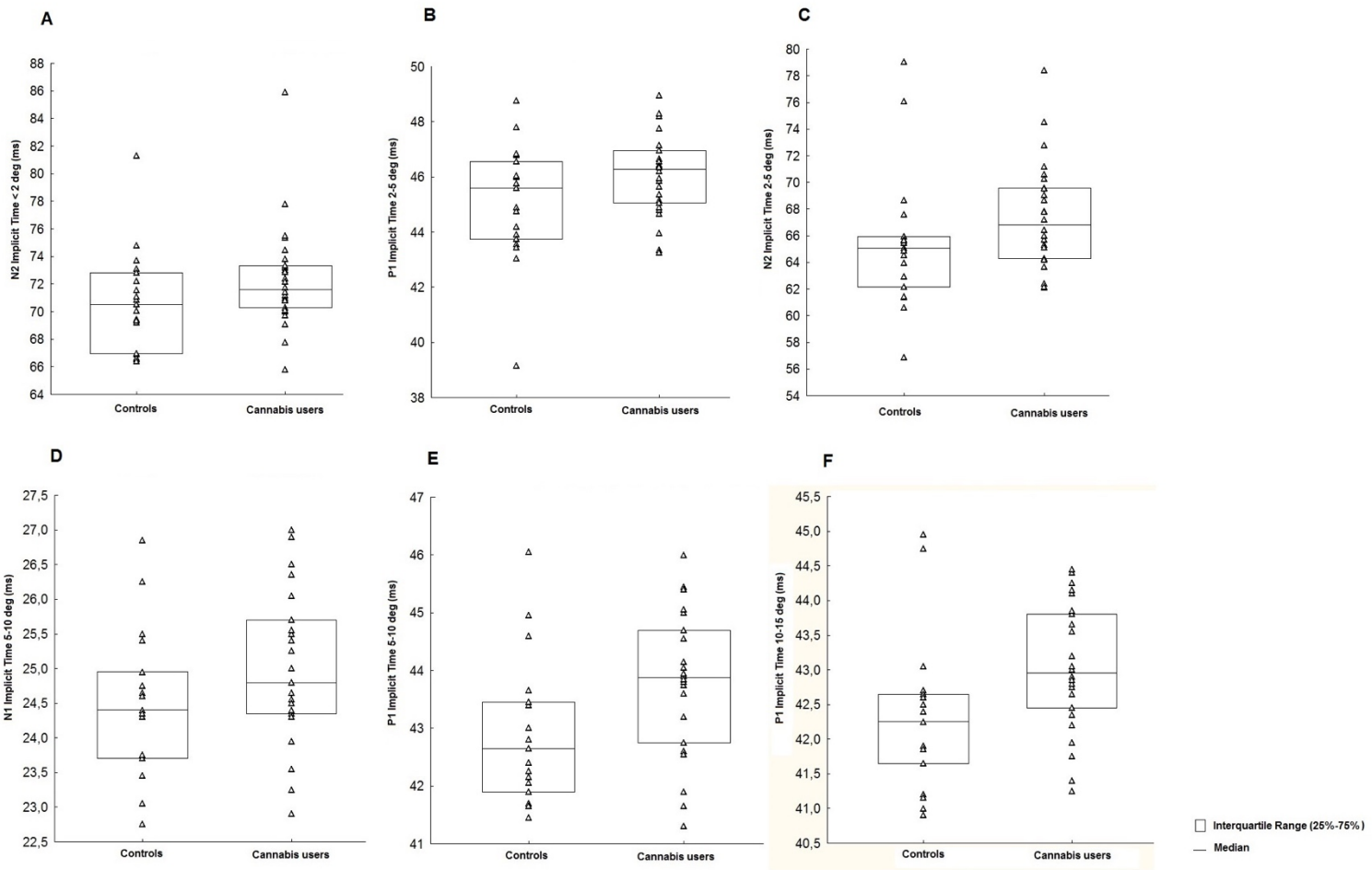


Figure 19 :

Figure 19A. Boîte à moustaches représentant le temps de culmination de N2 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 1 (<2 degrés), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec les médianes. Les utilisateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,037).

Figure 19B. Boîte à moustaches représentant le temps de culmination de P1 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 2 (2-5 degrés), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec des médianes. Les consommateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,046).

Figure 19C. Boîte à moustaches représentant le temps de culmination de N2 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 2 (2-5 degrés), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec des médianes. Les consommateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,018).

Figure 19D. Boîte à moustaches représentant le temps de culmination de N1 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 3 (5-10 degrès), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec des médianes. Les consommateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,034).

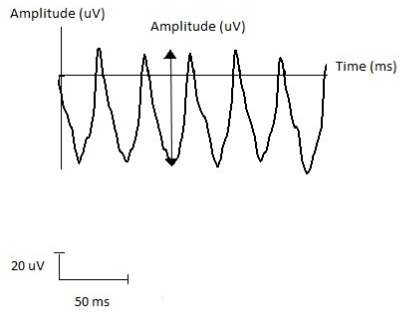
Figure 19E. Boîte à moustaches représentant le temps de culmination de P1 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 3 (5-10 degrès), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec des médianes. Les consommateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,006).

Figure 19F. Boîte à moustaches représentant le temps de culmination de P1 (ms) de l'électrorétinogramme multifocal (mfERG) dans l'anneau 4 (10-15 degrés), pour les consommateurs de cannabis (n = 49) et les témoins (n = 21) avec médiane. Les consommateurs de cannabis ont montré un temps de culmination augmenté et la différence entre les groupes est significative (p = 0,014).

INTERET DE NOUVELLES MESURES BASEES SUR LE BRUIT DE FOND RETINIEN

L'étude de l'activité neuronale de fond, ou bruit de fond, ie -en l'absence de la stimulation- est une approche qui pourrait permettre d'explorer la neurotoxicité du cannabis et de l'alcool. Les résultats préliminaires ont montré que le Δ9-THC provoque une augmentation du bruit de fond neuronal dans le cerveau. Les neurones du cerveau et de la rétine possèdent un système de neurotransmission et des propriétés anatomiques et fonctionnelles qui présentent des similarités. Cette étude analyse le bruit de fond de la rétine dans une population de consommateurs réguliers de cannabis et d'alcool.

Nous avons enregistré l'ERG flash de 26 contrôles sains et 45 consommateurs réguliers de cannabis, séparés en deux groupes en fonction de leur consommation d'alcool: inférieure ou égale à 4 verres standard par semaine (CU ≤ 4) ou strictement supérieure à 4 verres par semaine (CU > 4). Afin d'extraire le bruit de fond, nous avons calculé la transformée de Fourier des signaux pseudopériodiques et sinusoïdaux de la séquence flicker 3,0 ERG. Cette séquence représente la transmission verticale du signal des cônes aux cellules bipolaires. L'amplitude du bruit de fond est définie comme la moyenne des magnitudes des deux harmoniques avoisinantes: harmonique -1 (bruit à basse fréquence) et harmonique + 1 (bruit à haute fréquence).



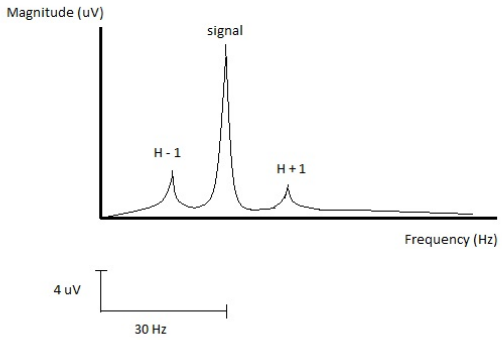


Figure 20 : Tracé typique de fERG, série flicker 3.0 et tracé obtenu après Analyse de Fourier. La magnitude de bruit est définie comme la moyenne de la magnitude aux deux fréquences voisines H-1 et H+1.

L'amplitude de l'harmonique -1 a été significativement augmentée entre les groupes CU > 4 (6,78 (+/-1,24)) et CU ≤ 4 (5,69 (+/-1,80)) chez les utilisateurs réguliers de cannabis et d'alcool. Une augmentation significative de l'amplitude moyenne des deux harmoniques a été observée entre les groupes CU > 4 (5,12 (+/-0,92)) et CU ≤ 4 (4,36 (+/-1,14)). Aucune différence significative n'a été observée en ce qui concerne l'amplitude de l'harmonique + 1.

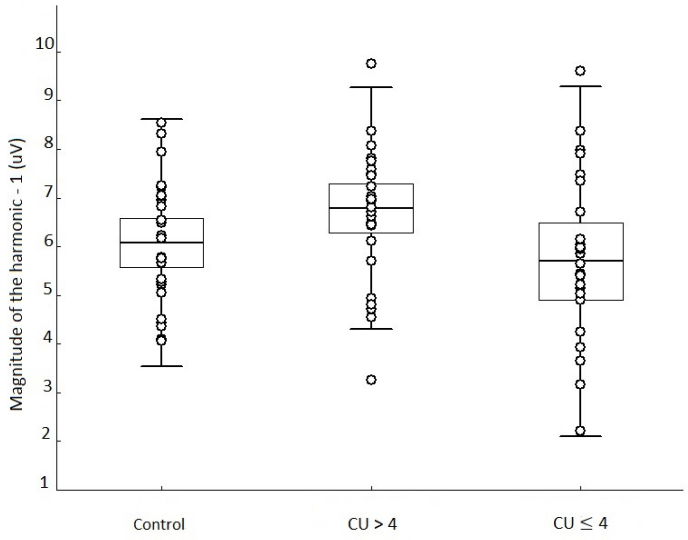


Figure 21 : Boîte à moustaches de la magnitude de l'harmonique-1 pour les utilisateurs de cannabis avec > et ≤ 4 consommations d'alcool/semaine et pour les contrôles avec la moyenne et l'écart-type. Pour les contrôles: n = 26; moyenne: 6, 07 µV; DS +/-1, 27. Pour CU > 4: n = 24; moyenne: 6, 78 µV; DS +/-1, 24. Pour CU ≤ 4: n = 21; moyenne: 5, 69 µV; DS +/-1, 80. Les petits disques représentent les données individuelles.

L'augmentation du bruit de fond peut refléter la neurotoxicité du cannabis, majorée par la consommation d'alcool, sur la dynamique des neurones rétiniens. Cette perturbation neuronale peut être attribuable à une libération altérée de neurotransmetteurs dans la rétine.

Encadrement et publication

Encadrement :
Alice Lucas et Audrey Thirion (thèse de médecine, DES de Psychiatrie)
Alice Lucas (Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2018)

Publication :

Lucas A, Thirion A, Schwan R, Krieg J, Angioi-Duprez K, Laprevote V, Schwitzer T.
Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use.
Prog Neuropsychopharmacol Biol Psychiatry. 2018 Oct 4.

3. Potentielles modulations de la libération synaptique rétinienne de neurotransmetteurs par le cannabis et intérêt des développements de nouveaux indicateurs de neurotransmission rétinienne

Dans le SNC, la modulation de la transmission synaptique induite par les exocannabinoïdes est médiée par le système endocannabinoïde, notamment les récepteurs cannabinoïdes, les ligands et les enzymes (Mechoulam et Parker, 2013). Ce système est situé dans des neurones impliqués dans la transmission synaptique centrale excitatrice et inhibitrice (Mechoulam et al., 2007; Mechoulam et Hanus, 2000; Mechoulam et Parker, 2013; Pertwee et al., 2010). Plus précisément, il se situe dans les neurones impliqués dans les voies de neurotransmission GABAergique (Caballero-Florán et al., 2016; Szabo et al., 2002, 1998), glutamatergique (Auclair et al., 2000; Kim et Thayer, 2000; Robbe et al., 2000). , 2001) et dopaminergique (Wu et French, 2000) et relaie les effets des exocannabinoïdes sur le fonctionnement du SNC. Appartenant au SNC, la rétine est dotée d'un système de neurotransmission complexe, notamment des voies dopaminergiques, glutamatergiques et GABAergiques (Hoon et al., 2014). En raison de la distribution anatomique de ces voies dans la rétine et de leur rôle dans le traitement de l'information visuelle au niveau rétinien, nous pouvons supposer que les exocannabinoïdes modulent le traitement de l'information au niveau rétinien et induisent des dysfonctionnements rétiniens, comme ceux observés avec les mesures électrophysiologiques.

Dans ce contexte, et afin d'évaluer de manière précise les voies rétiniennes de neurotransmission qui peuvent sous tendre les anomalies rétiniennes observées chez les usagers réguliers de cannabis, nous avons dérivé et évalué un certain nombre d'indicateurs rétiniens à partir des données rétiniennes précédemment enregistrées. C'est notamment le cas des potentiels oscillatoires rétiniens dont l'origine est les cellules amacrines rétiniennes qui sont des cellules dopaminergiques influencées par les modulations des voies rétiniennes dopaminergiques. D'autres indicateurs ont été dérivés et évalués : Rapport P50/N95, Complexité de Lempel-Ziv, onde PhNR, onde i (travaux en cours).

Encadrement et publication

Encadrement :

Ludovic Polli (Master 1 Sciences-Technologie-Santé, UL)
Guiné Jean-Baptiste (Master 1 Sciences-Technologie-Santé, UL)
Xenia Gordon (Master 1 Sciences-Technologie-Santé, UL)
Marianne Menigoz (Master 1 Sciences-Technologie-Santé, UL)
Florian Wencker (Master 1 Sciences-Technologie-Santé, UL)
Laura Malbos (Master 1 Sciences-Technologie-Santé, UL)
Maxence Rigon (Master 1 Sciences-Technologie-Santé, UL)
Yanis Menzer (Master 1 Sciences-Technologie-Santé, UL)

2 Publications en préparation

II. PERSPECTIVES SCIENTIFIQUES

1. Intérêt de la rétine en neurosciences

La rétine est un site extrêmement propice à l'étude du fonctionnement du cerveau dans les recherches en neurosciences (Bernardin et al., 2017; Garcia-Martin et al., 2014; Laprevote et al., 2015; Lavoie et al., 2014c; Londres. et al., 2013; Schwitzer et al., 2017b, 2015a). En raison de son origine embryologique, la rétine est une extension anatomique et développementale du SNC (Hoon et al., 2014). La rétine et le cerveau sont reliés entre eux par le nerf optique, composé des axones des cellules ganglionnaires, cellules qui sont le stade rétinien final du traitement de l'information et le plus intégré (Hoon et al., 2014). La rétine est composée de couches de neurones spécialisés qui sont interconnectés par des synapses et sous l'influence d'un système de neurotransmission complexe (Hoon et al., 2014), comme c'est le cas dans le cerveau. Ces neurones rétiniens partagent plusieurs propriétés anatomiques et fonctionnelles avec les neurones du cerveau (Hoon et al., 2014). Par exemple, les neurotransmetteurs dopaminergiques, sérotoninergiques, glutamatergiques, cholinergiques et GABAergiques sont des molécules clés impliquées dans la transmission synaptique rétinienne.

Publication

Publication :

Schwitzer T, Schwan R, Bubl E, Lalanne L, Angioi-Duprez K, Laprevote V.
Looking into the brain through the retinal ganglion cells in psychiatric disorders: A review of evidences.
Prog Neuropsychopharmacol Biol Psychiatry. 2017 Mar 20;76:155-162.

2. Pertinence des explorations électrophysiologiques rétiniennes dans les troubles neuropsychiatriques et addictifs

La rétine représente la première étape du traitement de l'information visuelle lorsque la lumière pénètre dans les yeux et représente donc une partie du système nerveux central facilement accessible. La fonction rétinienne n'est pas sous l'influence de fonctions cognitives de haut niveau - l'attention par exemple - comme c'est le cas lorsque le traitement visuel cortical est enregistré. Le fonctionnement de la rétine est une fonction bien étudiée à ce jour (Hoon et al., 2014). Les mesures dédiées au traitement de l'information au niveau rétinien sont bien standardisées, ce qui permet une bonne reproductibilité (Holder et al., 2010). Les tests électrophysiologiques peuvent être utilisés seuls ou associés entre eux, permettant d'évaluer avec précision le fonctionnement de la rétine. À l'aide de ces examens, l'étude de la fonction rétinienne est relativement rapide, peu coûteuse et facile à mener. Les dispositifs d'enregistrement de la fonction rétinienne peuvent être mobiles et petits. Les anomalies de la fonction rétinienne évaluées par des mesures électrophysiologiques rétiniennes sont présentes dans de nombreux troubles neuropsychiatriques (Lavoie et al., 2014d; Schwitzer et al., 2017b, 2015a; Silverstein et Rosen, 2015). Bien que la majorité de ces études soit réalisée sur de petits échantillons et que la spécificité de ces marqueurs reste à confirmer, les paramètres extraits des mesures électrophysiologiques rétiniennes peuvent être des candidats pertinents pour une utilisation en tant qu'indicateurs d'altérations fonctionnelles de troubles neuropsychiatriques tels que la schizophrénie, le trouble bipolaire, le trouble dépressif, les troubles neurodégénératifs, pour ne citer qu'eux. Plus spécifiquement, l'ERG flash peut être utilisé pour examiner les anomalies de neurotransmission dans les troubles neuropsychiatriques. Lavoie et al. (Lavoie et al., 2014a) ont montré que des altérations de la neurotransmission centrale de la dopamine et de la sérotonine - deux neurotransmetteurs impliqués dans la physiopathologie des troubles neuropsychiatriques et addictifs - affectaient les réponses à l'ERG flash chez la souris. L'ERG flash peut également fournir des marqueurs fonctionnels précoces et spécifiques du risque de développer des troubles neuropsychiatriques. Chez les jeunes enfants non atteints et non traités mais avec un risque génétique élevé de troubles neuropsychiatriques, une anomalie électrorétinographique spécifique a été

observée dans la réponse rétinienne des bâtonnets (Hébert et al., 2010). De plus, des modifications des paramètres de l'ERG flash, comme le montre l'altération du temps de culmination de l'onde b enregistrée en condition scotopique, ont été observées chez des souris après un traitement prolongé par du lithium, un stabilisateur de l'humeur fréquemment utilisé dans le trouble bipolaire, indiquant que l'ERG flash pourrait fournir des marqueurs fonctionnels pertinents de l'évaluation des traitements pharmacologiques (Lavoie et al., 2015).

Publication

Publication :

Schwitzer T, Schwan R, Bernardin F, Jeantet C, Angioi-Duprez K, Laprevote V. 2016. Commentary: Anatomical constitution of sense organs as a marker of mental disorders. Front. Behav. Neurosci. 10, 56.

3. Poursuite des recherches sur l'impact du cannabis sur la rétine

Nous poursuivons les travaux de recherche sur l'impact de l'usage de cannabis sur le traitement rétinien, en mesurant notamment si les délais de traitement que nous avons observés sont modifiés après l'arrêt du cannabis et comment ils évoluent tout au long de la période de sevrage au cannabis et à l'arrêt du cannabis. Cette question fait l'objet du programme MACBETH que je coordonne. Dans ce projet, les participants répartis en deux groupes de 20 se voient proposer une aide à l'arrêt du cannabis et suivent un programme de méditation de pleine conscience de 8 semaines ou le suivi habituellement proposé. Des mesures de la fonction (et de la structure) rétinienne, basées sur l'ERG flash, pattern, et multifocal, sont réalisées tout au long de la période de sevrage et après l'arrêt du cannabis pour les participants ayant arrêté le cannabis.

Encadrement et financement

Encadrement :
Majda Arfa (thèse de médecine, DES de Psychiatrie)

Financement:
Projet MAC BETH (Méditation de Pleine Conscience et Cannabis : efficacité thérapeutique), Appel à projets jeunes chercheurs GIRCI EST

4. Intérêt dans les usages réguliers d'alcool et de tabac

Dans le cadre du projet Causa Map, nous avons observé un effet sur le fonctionnement rétinien chez les usagers réguliers de cannabis. Ces usagers sont également des consommateurs réguliers de tabac et d'alcool pour la plupart, compliquant ainsi l'attribution de cet effet directement au cannabis. Bien que nos analyses nous aient orientés vers un effet principal du cannabis, il nous paraissait important d'évaluer de manière directe l'impact des consommations régulières de tabac et d'alcool sur le fonctionnement rétinien. A notre connaissance, aucune étude n'a évalué à ce jour l'effet des consommations régulières de tabac et d'alcool sur le fERG, le PERG et le mfERG. Dans le cadre du projet Causa Map, un groupe contrôle d'usagers de tabac est en cours de recrutement pour évaluer l'effet direct des consommations régulières de tabac sur la fonction rétinienne en comparaison à une population de volontaires sains. Pour l'alcool, un financement de la Fondation pour la Recherche en Alcoologie a été obtenu pour cette étude qui vise à évaluer l'effet direct des consommations régulières d'alcool sur la fonction rétinienne en comparaison à une population de volontaires sains à l'aide de mesures de fERG, de PERG et de mfERG.

Encadrement et financement

Encadrement :
Ludovic Polli (Master 2 de biologie intégrative et Physiologie, Université Paris VI)
Eloïse Finiels (Master 1 Sciences-Technologie-Santé, Iniversité de Lorraine)

Financement:
ERICA : Fondation pour la Recherche en Alcoologie (FRA), 2018

5. Intérêt dans le trouble dépressif majeur

Il existe aujourd'hui un certain nombre d'arguments pour dire que des anomalies de la fonction rétinienne sont retrouvées dans le trouble dépressif majeur. Dans le cadre du projet Lumidep, nous allons réaliser une évaluation complète de la fonction rétinienne avec le fERG, le PERG et le mfERG, ainsi que des mesures spécifiques que nous avons développées telles que le bruit de fond rétinien, chez des patients souffrant de troubles dépressifs majeurs. Ces évaluations vont nous permettre de confirmer les résultats de la littérature mais également de réaliser une évaluation standardisée et donc reproductible de la fonction rétinienne (et de la structure par OCT). Les patients répartis en deux groupes de 25 vont être randomisés dans un groupe bénéficiant du suivi habituel (pharmacothérapie et psychothérapie) et d'un traitement par luminothérapie dispensé par un dispositif portatif et donc facilement utilisable pendant les activités de la vie quotidienne ; et dans un groupe bénéficiant du suivi habituel (pharmacothérapie et psychothérapie) et d'un traitement par luminothérapie placebo. Ces évaluations rétiniennes vont être réalisées tout au long de la période de suivi des patients. Elles vont nous permettre de voir l'évolution de la fonction rétinienne (et de la structure) tout au long de la période de suivi et à la résolution de l'épisode dépressif. Ce projet bénéficie d'une double collaboration industrielle avec MétroVision qui nous fournit le matériel ERG et Lucimed qui a produit le dispositif de Luminothérapie. Le recrutement à débuté récemment.

Encadrement, publication et financement

Encadrement :
Eve Cosker (thèse d'université, Ecole doctorale des sciences de la vie et de la santé, Université de Strasbourg. 1ere inscription en novembre 2017)

Publication:
New insights on the role of the retina in diagnostic and therapeutic strategies in major depressive disorder
Eve Cosker, Raymund Schwan, Karine Angioi-Duprez, Anne Giersch, Vincent Laprévote, Thomas Schwitzer
Soumis à Neuroscience and Biobehavioral Reviews

Financement:
LUMIDEP: financement Lucimed

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ACTIVITES D'ENCADREMENT

- **Thèse d'Université**

Eve Cosker : Co-direction avec le Pr Raymund Schwan. Ecole doctorale des sciences de la vie et de la santé, Université de Strasbourg. 1ere inscription en novembre 2017. Sujet : Evaluation de l'impact d'un épisode dépressif caractérisé sur le fonctionnement rétinien par la mesure de l'électrorétinogramme, et de l'impact de la luminothérapie par Luminette sur le fonctionnement rétinien et cognitif.

New insights on the role of the retina in diagnostic and therapeutic strategies in major depressive disorder

Eve Cosker, Raymund Schwan, Karine Angioi-Duprez, Anne Giersch, Vincent Laprévote, Thomas Schwitzer

Soumis à Neuroscience and Biobehavioral Reviews

- **Master 2**

Ludovic Polli, Master 2 de Biologie Intégrative et Physiologie, Université Paris VI, 2019 : Etude de la fonction rétinienne à l'aide de l'électrorétinogramme chez les usagers réguliers d'alcool (ERICA)

Claire Jansen : Co-encadrement avec le Dr Vincent Laprévote, Master 2 de Biologie Intégrative et Physiologie, Université Paris VI, 2018. Sujet : Traitement des fréquences spatiales visuelles des visages dans la schizophrénie : une étude en électrophysiologie.

A review on dynamic of the spatial frequency integration during face perception in patient with schizophrenia

En préparation

Eve Cosker : Co-encadrement avec le Dr Vincent Laprévote, Master 2 de Biologie Intégrative et Physiologie, Université Paris VI, 2017. Sujet : Impact des variants génétiques du système endocannabinoïde sur les marqueurs électrophysiologiques rétiniens chez les usagers réguliers de cannabis

Cosker E, Schwitzer T, Ramoz N, Ligier F, Lalanne L, Gorwood P, Schwan R, Laprévote V. The effect of interactions between genetics and cannabis use on neurocognition. A review. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Mar 2;82:95-106.

Maxence Rigon, Co-encadrement avec le Dr Vincent Laprévote, Master 2 de Biologie Intégrative et Physiologie, Université Paris VI, 2016. Sujet : Electrophysiologie rétinienne dans la schizophrénie.

- **Master 1**

Eloïse Finiels, Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2019. Sujet : Etude du lien entre antidépresseurs et altérations rétiniennes dans le trouble dépressif majeur

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Lucas A, Thirion A, Schwan R, Krieg J, Angioi-Duprez K, Laprevote V, Schwitzer T.

Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use.

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Xenia Gordon : Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2017. Sujet : Etude de la complexité de Lempel-Ziv extraite de la fonction rétinienne chez les usagers réguliers de cannabis

Marianne Menigoz : Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2017. Etude de la complexité de Lempel-Ziv extraite de la fonction rétinienne chez les usagers réguliers de cannabis

Florian Wencker : Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2016. Etude du rapport P50/N95 issu de l'électrorétinogramme pattern chez les usagers réguliers de cannabis

Laura Malbos : Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2016. Etude des potentiels oscillatoires de l'électrorétinogramme flash chez les usagers réguliers de cannabis

Maxence Rigon : Master 1 Sciences-Technologie-Santé, Université de Lorraine, 2014. Sujet : Electrophysiologie rétinienne dans la schizophrénie

- **Thèses de Médecine (uniquement celles avec publications)**

Alice Lucas et Audrey Thirion, 2018. Sujet : Association entre le bruit de fond rétinien et l'usage régulier et co-occurrent d'alcool et de cannabis

Lucas A, Thirion A, Schwan R, Krieg J, Angioi-Duprez K, Laprevote V, Schwitzer T.

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Prog Neuropsychopharmacol Biol Psychiatry. 2018 Oct 4.

Daphné Sarre et Marie-Laure Henrion, 2019. Sujet : Localisation spatiale des anomalies rétiniennes chez les usagers réguliers de cannabis : pertinence de l'électrorétinogramme multifocal

Schwitzer T, Henrion ML, Sarre D, Albuisson E, Angioi-Duprez K, Giersch A, Lalanne L, Schwan R, Laprevote V. Spatial localization of retinal anomalies in regular cannabis users: the relevance of the multifocal electroretinogram. Schizophrenia Research. In press (IF: 3.96)

Mohammed Lakhliphi, 2019. Sujet : Troubles de l'exploration visuelle chez les patients souffrant de schizophrénie

Scanpath in schizophrenia: A review of the findings and therapeutic perspectives

Mohammed Lakhlifi, Vincent Laprevote, Karine Angioi-Duprez, Laurence Lalanne, Raymund Schwan, Thomas Schwitzer

En préparation

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FINANCEMENTS

Projets dotés d'un financement public (PHRC…)

- Financement Fondation pour la Recherche en Alcoologie (FRA), 2018
  Investigateur principal
  Projet ERICA (Etude de la fonction rétinienne à l'aide de l'électrorétinogramme chez les usagers réguliers d'alcool)
  Montant 8 k€

- Financement Ecole Polytechnique Paris, 2017
  Investigateur principal
  Projet POETESS (Psychiatric and Ophthalmic Early TelE Symptoms Screaning)
  Montant 250 k€

- Appel à projets jeunes chercheurs GIRCI EST, 2015
  Investigateur principal associé
  Projet MAC BETH (Méditation de Pleine Conscience et Cannabis : efficacité thérapeutique)
  Montant 40 k€

Projets dotés d'un financement associatif ou privé.

- Financement Fondation Roger de Spoelberch, 2018
  Investigateur principal
  Projet POETESS (Psychiatric and Ophthalmic Early TelE Symptoms Screaning)
  Montant 50 k€

- Financement Lucimed (Belgique), 2016
  Investigateur principal
  Projet LUMIDEP (Etude de l'efficacité d'un dispositif portatif de luminothérapie dans le trouble dépressif majeur)
  Montant 25 k€

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PROJETS

Mes recherches portent sur le traitement rétinien comme modèle d'étude du fonctionnement cérébral dans les troubles psychiatriques et addictifs au sein de l'équipe du Professeur Schwan et du Pr Vincent Laprévote. Cette thématique a été renforcée par notre intégration courant 2018 à l'équipe INSERM 1114 Neuropsychologie cognitive et physiopathologie de la schizophrénie (Dr Anne Giersch). Au sein de cette unité, je coordonne maintenant les recherches menées sur la rétine. Ces recherches sont menées en étroite collaboration avec le Pr Laurence Lalanne.

Le projet de recherche que je souhaite mener dans les années à venir vise à l'utilisation de la rétine comme porte d'entrée du fonctionnement du cerveau pour l'étude de la physiopathologie dans les troubles psychiatriques et addictologiques mais également pour le développement de marqueurs rétiniens de diagnostic, de dépistage des populations à risque, et d'orientation et d'évaluation thérapeutique.

Pour cela, nous avons développé avec le Pr Raymund Schwan et le Pr Valérie Loui-Dorr (Ecole Nationale Supérieur d'Electricité et de Mécanique à Nancy, spécialiste dans le traitement du signal) un dispositif médical utilisant ces mesures rétiniennes. Nous travaillons en étroite collaboration avec les spécialistes de l'analyse du signal du Centre de Recherche en Automatique de Nancy (CRAN) afin de développer des méthodes d'exploration de la transmission du signal rétinien au cerveau. Ces travaux se font également en partenariat avec l'industriel français qui produit ces matériels de mesure (Métrovision, Pérenchies, France).

Ce projet est soutenu par X-UP, l'incubateur de l'école Polytechnique Paris. Ce dispositif propose de combiner la stimulation rétinienne, l'amplification, l'acquisition, l'analyse automatisée intégrée ou à distance des résultats, et la comparaison automatisée aux normes de la fonction et de la structure rétiniennes. Le dispositif en cours de développement est particulièrement destiné à la mesure de la fonction et de la structure rétiniennes en pratique courante de médecine. Il est adapté au centre de détection et de dépistage des troubles psychiatriques.

POETESS
Psychiatric and Ophthalmic Early TelE Symptoms Screaning

Valorisation, financement et encadrement

Valorisation :
1 brevet déposé le 28 février 2018 (FR 18/00175) sur un dispositif médical intégrant des mesures ophtalmologiques en santé mentale. Thomas Schwitzer 35%, Raymund Schwan 35%, Valérie Louis-Dorr 30%,

Financement:
Financement et Collaboration Ecole Polytechnique Paris & Financement Fondation Roger de Spoelberch

Encadrement :
Maxime Ortenzi : ENSEM Nancy (Ecole Nationale Supérieure d'Electricité et de Mécanique)

Contexte :

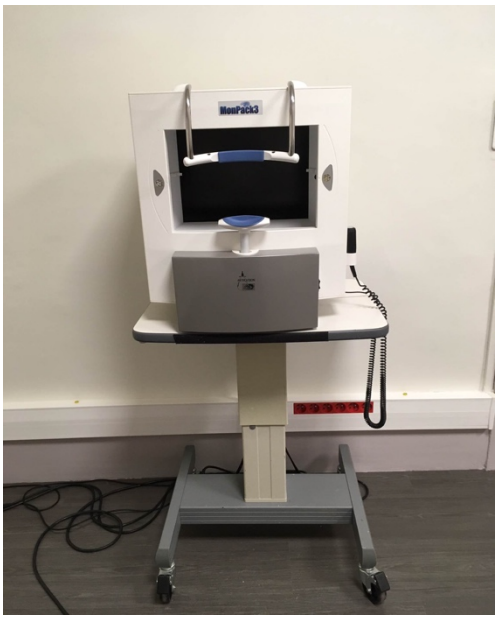
Afin de pouvoir développer des marqueurs fonctionnels présentant les critères requis pour une large utilisation, il apparaît pertinent d'étudier de manière indirecte le fonctionnement cérébral. Les acquisitions électrophysiologies sont des mesures qui d'une part sous-tendent les activités fonctionnelles cérébrales et qui, d'autre part, ont l'énorme avantage de posséder une résolution temporelle qui est à l'échelle des processus cérébraux à étudier. Ces nouvelles approches pourraient permettre de surpasser la difficulté d'approcher directement le fonctionnement cérébral en étudiant de manière indirecte les mécanismes cérébraux sous-tendant l'apparition des troubles mentaux. Ces approches pourraient fournir des marqueurs diagnostiques, des marqueurs de risque de maladies psychiatriques et enfin des marqueurs d'orientation et d'évaluation thérapeutiques.

La rétine est un excellent site d'investigation du fonctionnement cérébral car la rétine appartient au système nerveux central en raison de son origine embryologique. C'est la voie d'entrée de la perception visuelle et donc de la voie visuelle ventrale. Son lien anatomique et fonctionnel avec de nombreuses structures cognitives est d'ores et déjà établi. Elle représente une extension anatomique et développementale du cerveau et est reliée au cerveau par le nerf optique formé par les axones des cellules rétiniennes ganglionnaires. L'étude de la fonction rétinienne donne l'unique opportunité d'étudier de manière objective un réseau neuronal complexe disposé en étages qui sont en lien avec les structures cérébrales. La rétine est composée de nombreuses couches cellulaires neuronales impliquées dans le traitement rétinien de l'information visuelle et dont il existe pour la plupart des méthodes permettant d'étudier leurs propriétés fonctionnelles avec une grande précision. Cette structure est composée de neurones rétiniens disposés en couches cellulaires : les couches nerveuses rétiniennes. Ces neurones rétiniens partagent des similarités anatomiques et fonctionnelles avec les neurones cérébraux. Ils sont notamment dotés d'un système de neurotransmission complexe composés des principaux neurotransmetteurs présents dans le cerveau et impliqués dans la physiopathologie des troubles psychiatriques et addictifs : dopamine, sérotonine, noradrénaline, glutamate, gaba, par exemple.

En plus du fait que la rétine est facilement accessible, ces techniques électrophysiologiques sont dotées de protocoles standardisés pouvant être répliqués par les différentes équipes et assurant la reproductibilité des résultats. Si ces méthodes sont assez exploitées dans le domaine de l'ophtalmologie car elles permettent le diagnostic de certaines pathologies des structures rétiniennes elles sont peu ou pas présentes en psychiatrie clinique. Or ces techniques sont particulièrement adaptées à la recherche en psychiatrie, ainsi qu'à une large utilisation à des fins de dépistage, puisque ces protocoles sont simples, rapides, non invasifs et peu onéreux. En mesurant les activités électrophysiologiques de différentes populations neuronales rétiniennes, l'ERG pourrait nous permettre d'approcher le fonctionnement et les anomalies de neurotransmission à l'origine, en partie, des troubles psychiatriques. L'utilisation de l'ERG pour détecter les anomalies de neurotransmission dans les troubles psychiatriques est une approche rare et

innovante. En France, nous sommes la seule équipe ayant l'expertise dans ce champ de développement et dans le monde, seules quelques équipes se sont spécialisées dans ce domaine. L'ERG permet d'enregistrer l'activité électrique des neurones rétiniens sous la forme d'un potentiel moyen électrophysiologique qui permet de quantifier la réponse cellulaire totale ou partielle (population de neurones) et donc la réponse fonctionnelle de ces cellules. Cette réponse peut permettre d' identifier les anomalies de neurotransmission centrale.

Etat actuel de l'art et de la technologie :



Les potentiels, la fonction et la structure rétinienne sont traditionnellement mesurés dans une salle spécifiquement aménagée par deux dispositifs séparés. Ces dispositifs sont volumineux, nécessitent une installation électrique spécifique et coûteuse, augmentent le temps de préparation et de mesure pour le sujet et ne sont donc présents que dans les centres spécialisés dédiés aux mesures électrophysiologiques. Le dispositif de mesure de la fonction rétinienne comprend des éléments fixes distincts : un appareil de stimulation de la fonction rétinienne (par électrorétinogramme flash, pattern et multifocal), un appareil d'acquisition du signal électrique rétinien, une chaine d'amplification du signal, une connexion pour transférer des données vers l'ordinateur, un logiciel avec modules d'analyse de la fonction rétinienne adaptés au différents ERGs, obtenus avec différents pattern de stimulation, une analyse semi-automatisée des biomarqueurs caractéristiques des différents ERGs.

La réalisation d'un électrorétinogramme est faite dans des services spécialisés de neurophysiologie clinique ou d'ophtalmologie. Pour que les pupilles de la personne présentent l'état de dilatation nécessaire à la réalisation de l'examen, celui-ci est placé dans l'obscurité pendant une période d'adaptation de vingt à trente minutes, avant qu'un opérateur ne pose sur son visage, grâce à un éclairage de faible puissance, des électrodes nécessaires à l'examen. Ces électrodes comprennent une ou plusieurs électrodes de mesure, qui peuvent être posées sur la cornée, sur la peau de la paupière inférieure, dans le cul-de-sac conjonctival et des électrodes de référence, qui sont habituellement posées sur le front et au lobe de chaque oreille. Après la pose de ces électrodes, la personne est placée devant l'électrorétinographe, qui est un dispositif permettant l'émission de stimulations telles que des flashs lumineux ou des stimulations lumineuses à géométrie variable, de préférence en champ total, et de mesurer, par le biais des différentes électrodes, la réponse électrophysiologique de la rétine à ces stimulations lumineuses. Il est également nécessaire, pour pratiquer cet examen, de prévoir une pièce réservée à l'adaptation de la personne à l'obscurité. Enfin, une installation électrique spécifique doit également être mise en place pour le branchement de cet électrorétinographe. En conséquence, les électrorétinogrammes ne sont pratiqués que pour des indications spécifiques.

Il s'avère ainsi avantageux de posséder un dispositif portatif, peu couteux ne nécessitant pas un aménagement particulier d'un salle d'examen et qui réalise les examens de manière automatisée avec une interprétation et validation médicale des résultats des mesures à distance (plateforme).

Objectifs du projet POETESS :

Nous sommes en train de développer un dispositif qui ressemble à des lunettes de réalité virtuelle. Le dispositif en cours de développement permet de remédier à ces inconvénients en proposant un dispositif intégré combinant une paire de lunettes virtuelles, la mesure de la fonction rétinienne et la mesure de la structure rétinienne. Ce dispositif propose de combiner des stimulations rétiniennes spécifiques, l'amplification, l'acquisition, l'analyse automatisée intégrée ou à distance des résultats, et la comparaison automatisée aux normes de la fonction et de la structure rétiniennes. Ce dispositif ne nécessite pas d'aménagements spécifiques des locaux destinés à la mesure. Son utilisation n'est donc pas restreinte aux centres spécialisés. Ce dispositif peut être réalisé en combinaison avec des électrodes sèches.

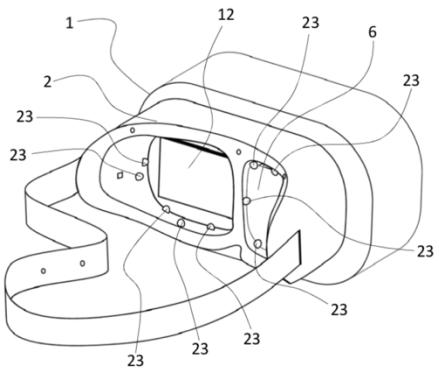


Figure : Dispositif d'exploration rétinienne développé par Schwitzer T, Schwan R, & Louis Dorr V. Esquisse issue de la demande de brevet (déposée en février 2018 par l'Université de Lorraine, France).

Figure : Test de notre premier prototype de stimulation et d'acquisition du signal rétinien par paire de lunettes de réalité virtuelle par notre ingénieur recherche (avril 2018)

Le dispositif en cours de développement est particulièrement destiné à la mesure de la fonction et de la structure rétinienne en pratique courante de médecine. Il est basé sur des protocoles de stimulation déjà existants et validé scientifiquement pour l'ERG et les PEV. Ces protocoles sont recommandés par l'International Society for Clinical Electrophysiology of Vision (ISCEV). Ils sont donc valides, reproductibles et avec une portée internationale. Ces protocoles ont déjà prouvé leur utilité, utilisés seuls ou en association, dans l'aide au diagnostic de pathologies ophtalmologiques.

Le dispositif en cours de développement comprend :

- Analyse automatisée de la fonction rétinienne et de ses structures (dans un deuxième temps du développement) basée sur la mesure de potentiels EEG et ERG lors de protocoles déterminés de stimulation visuelle chez les patients présentant un trouble psychiatrique
- Appareil de stimulation visuelle rétinienne, d'acquisition et d'amplification ERG et EEG, et logiciel d'analyse et de comparaison automatisées aux normes de la fonction rétinienne chez les patients présentant un trouble psychiatrique

Ce dispositif permet de résoudre un certain nombre de freins à la large diffusion d'outils de diagnostic et à la détection et au dépistage précoce de maladies notamment neuropsychiatriques.

Il permet en outre :

- La facilité de la réalisation des examens, la maniabilité, et la mobilité du dispositif permettant d'être utilisé par des professionnels non formés à ces techniques d'examens électrophysiologiques et par des professionnels formés en demande
- La large diffusion et la réalisation plus rapide d'examens habituellement réalisés uniquement dans des centres spécialisés et non par les consultations de médecins libéraux
- La possibilité d'accessibilité aux examens dans les déserts médicaux
- La réalisation automatisée d'examens nécessitant habituellement des locaux spécifiques, du temps de soignant et des compétences techniques spécifiques
- La réalisation simultanée d'examens électrophysiologiques de la rétine et du cerveau dont les informations additionnées sont indispensables au diagnostic de certitude
- L'analyse à distance des données avec interprétation des résultats pour le professionnel
- L'aide au diagnostic, au dépistage et à la détection précoce d'un nombre important de pathologies permettant ainsi une prise en charge précoce et la diminution des traitements invasifs et couteux
- Le suivi de l'efficacité des traitements

VALIDATION DES HYPOTHÈSES PHYSIOPATHOLOGIQUES

Afin d'étayer les hypothèses physiopathologiques que nous avons émises et qui pourraient sous-tendre les anomalies rétiniennes découvertes chez les patients souffrant de troubles psychiatriques et addictifs, nous avons, avec le Pr Raymund Schwan, constitué un consortium de recherche européen. Ce consortium réunit différentes équipes de recherche en Europe : l'équipe du Pr Lucas Giner (Université de Séville), celle du Pr Thome (Université de Rostock), celle du Pr Riemenschneider et du Pr E. Bubl (Université de Homburg/Sarr), celle du Dr David Hicks (Strasbourg). Nous avons déposé ensemble, à l'appel à projet ERA-NET NEURON 2017, un projet de recherche réunissant des mesures translationnelles basées sur la génétique, sur l'analyse post-mortem de rétines humaines, sur l'analyse moléculaire et électrophysiologique chez le rongeur et sur des mesures fonctionnelles rétiniennes chez l'homme. Ce projet, piloté depuis Nancy et dont je suis l'investigateur principal, n'a pas été sélectionné mais nous travaillons sur son amélioration en préparation d'une nouvelle soumission.

Objectifs et rationnels

Le trouble dépressif majeur (TDM) est l'une des maladies mentales les plus graves affectant des centaines de millions de personnes dans le monde. Bien qu'il soit actuellement classé comme la quatrième cause d'invalidité par l'Organisation Mondiale de la Santé, il est prévu qu'il deviendra la deuxième cause en 2020. À ce jour, on sait que la physiopathologie du TDM combine des facteurs génétiques, des déterminants environnementaux passés ou actuels, ainsi que des perturbations dans plusieurs voies de signalisation moléculaire (Charney et Matignon, 2004).
Le traitement actuel utilisé pour le TDM est une thérapie par antidépresseur seul ou en combinaison avec la psychothérapie. La pharmacothérapie dans le TDM cible principalement les voies de neurotransmission monoaminergique, telles que la dopamine, la sérotonine et la noradrénaline, ce qui suggère une implication potentielle de ces molécules dans la physiopathologie de ce trouble (Hamon et Blier, 2013). Une autre stratégie thérapeutique récente utilisée dans le TDM est la luminothérapie qui régule les rythmes circadiens à travers les voies

mélatoninergiques. Les résultats récents montrent son efficacité seule ou combinée à un traitement antidépresseur dans le TDM (Lam et al., 2016), suggérant un rôle des voies mélatoninergiques dans la physiopathologie du TDM. Les approches thérapeutiques pharmacologiques ou la luminothérapie sont généralement sûres, mais les bienfaits cliniques sont souvent observés après des semaines voire des mois d'administration. Par conséquent, il est urgent d'élaborer de nouvelles approches pour mieux accéder aux mécanismes de transmission synaptique impliqués dans la physiopathologie du TDM afin d'offrir de meilleures stratégies aux patients. Compte tenu du risque élevé de morbidité et de mortalité des patients atteints de TDM partiellement ou non traités, cela constitue actuellement une étape cruciale.

L'objectif de cette étude est de permettre une meilleure compréhension des dysfonctionnements de la transmission synaptique dans le TDM au niveau clinique, génétique et moléculaire. Ce projet est particulièrement novateur et pertinent puisqu'il utilise la rétine comme un accès indirect au cerveau fonctionnel afin d'améliorer la compréhension des anomalies de transmission synaptique du cerveau dans le TDM. La collaboration développée dans le cadre de ce projet permet d'utiliser des évaluations complémentaires de la rétine, telles que les mesures moléculaires, génétiques et fonctionnelles chez l'homme et l'animal, ainsi que dans la rétine post mortem.

Premier axe

Il est consacré à l'étude des modulations des voies de transmission synaptique impliquées dans le TDM, à savoir la sérotonine, la dopamine, la noradrénaline et la mélatonine, dans la rétine des modèles animaux de TDM.

Deux catégories de modèles animaux seront utilisées. Le premier groupe utilisera des états dépressifs induits par l'environnement chez les souris (Fonken et Nelson, 2013), et sera constitué par des souris chez lesquelles les niveaux de neurotransmetteurs monoaminergiques sont altérés.

Le deuxième groupe concernera les souris Arvicanthis (rongeurs diurnes) dont la rétine est riche en cônes et se rapprochera plus étroitement de la fonction maculaire centrale humaine (Boudard et al., 2010). On peut induire des états dépressifs chez cette espèce (Fonken et al., 2012), et l'utilisation de certains médicaments aura une incidence sur la neurotransmission monoaminergique.

Les rétines de tous les animaux seront examinées au niveau fonctionnel (fERG, PERG, mfERG) (Hubbard et al., 2015; Porciatti, 2007) et au niveau moléculaire (Gastinger et al., 2006). L'expression de la mélatonine sera dosée à la fois dans la glande pinéale et dans la rétine (GIANESINI et al., 2015).

Deuxième axe :

Il s'agit d'analyses moléculaires sur les voies de transmission synaptique impliquées dans la physiopathologie du TDM (dopamine, sérotonine, noradrénaline et mélatonine), qui seront effectuées sur des rétines post mortem collectées chez les victimes de suicide de sujets ayant souffert de TDM en comparaison à une collection de rétines de personnes décédées d'une autre cause que le suicide. Une procédure spécifique pour l'autopsie, la fixation, la conservation et l'analyse immunohistochimique a été décrite précisément dans la demande de financement.

Troisième axe :

Il est axé sur les mesures électrophysiologiques rétiniennes par flash (fERG), pattern (PERG) et multifocal (mfERG) ERG chez les patients souffrant de TDM. Les mesures d'ERG sont complémentaires et informent sur le fonctionnement de différents types de cellules rétiniennes. Comme ces cellules sont sous l'influence de systèmes de transmission synaptiques spécifiques, les modifications des mesures observées à l'ERG peuvent devenir de bons indicateurs des anomalies de transmission synaptique du cerveau dans le TDM (Schwitzer et al., 2015). Par exemple, le gain de contraste du PERG semble sensible aux changements de la transmission synaptique dopaminergique (Schwitzer et al., 2016). En effet, les

cellules amacrines dopaminergiques jouent un rôle clé dans le gain de contraste rétinien et cette mesure est altérée dans les troubles neurologiques impliquant des dysfonctionnements dopaminergiques tels que la maladie de Parkinson. Étant donné que des dysfonctionnements dopaminergiques sont suggérés dans la physiopathologie du TDM, les anomalies au PERG peuvent informer sur les déficits dopaminergiques chez les patients. En outre, les réponses rétiniennes enregistrées avec l'ERG Flash peuvent être sensibles à la transmission sérotoninergique. Il a été démontré que l'administration d'un antidépresseur médiateur des voies sérotoninergiques était associée à la fois à la rémission des symptômes dépressifs et à des modifications de l'amplitude de l'onde b du fERG (Schwitzer et al., 2015). Puisque l'onde b est un marqueur du fonctionnement des cellules bipolaires et considérant que les récepteurs de la sérotonine sont détectés dans les cellules bipolaires, cette constatation suggère que les mesures de fERG peuvent fournir de bons indicateurs des dysfonctionnements de la transmission synaptique sérotoninergique dans le TDM. De plus, Lavoie et al. ont montré que les souris Tph2-KI, qui ont une diminution de 80% de la sérotonine cérébrale, ont une augmentation du temps de culmination de l'onde b du fERG enregistré en condition photopique (Lavoie et al., 2014). Les modifications de la transmission synaptique sérotoninergique trouvées chez les patients TDM ou après l'administration de médicaments agissant sur cette voie de signalisation peuvent influencer les mesures du fERG.

Quatrième axe :

Cette partie se concentre sur les analyses génétiques en utilisant les endophénotypes mentionnés ci-dessus et générés par les mesures ERG comme des traits quantitatifs des patients avec TDM et des contrôles pour améliorer la compréhension des causes génétiques associées aux anomalies de transmission synaptique impliquées dans la physiopathologie du TDM.

Des études récentes d'associations génomiques (GWAS) n'ont pas réussi à identifier les polymorphismes de nucléotides simples (SNP) dans le TDM. Cet échec a été

principalement attribué à la grande hétérogénéité du phénotype "dépression", et l'absence à la fois de la puissance statistique et de la prise en compte du rôle de l'environnement.

L'objectif central de cet axe est l'élucidation des mécanismes génétiques associés aux différents ERGs (flash, pattern, multifocal) en tant que traits quantitatifs des patients atteints de TDM pour identifier les causes génétiques et les anomalies de transmission synaptiques impliquées dans la physiopathologie du TDM.

Acquérir une meilleure compréhension de la contribution génétique à tous les aspects du TDM doit être une priorité car elle fournira une plate-forme solide pour le développement de stratégies préventives et thérapeutiques futures.

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5 PUBLICATIONS REPRESENTATIVES

5 Publications représentatives

Schwitzer T, Schwan R, Angioi-Duprez K, Ingster-Moati I, Lalanne L, Giersch A, Laprevote V, 2015. The cannabinoid system and visual processing: A review on experimental findings and clinical presumptions. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 25, 100–112.

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REVIEW

The cannabinoid system and visual processing: A review on experimental findings and clinical presumptions

Thomas Schwitzer[a,b,d,e], Raymund Schwan[a,b,c,d], Karine Angioi-Duprez[f], Isabelle Ingster-Moati[g], Laurence Lalanne[h,i], Anne Giersch[e], Vincent Laprevote[a,b,c,d,*]

[a]EA7298, INGRES, Université de Lorraine, Vandœuvre-lès-Nancy F-54000, France
[b]Maison des Addictions, CHU Nancy, Nancy F-54000, France
[c]Centre d'Investigation Clinique CIC-INSERM 9501, CHU Nancy, Nancy F-54000, France
[d]Centre Psychothérapique de Nancy, Nancy F-54000, France
[e]INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg F-67000, France
[f]Service d'Ophtalmologie, CHU Nancy, Nancy F-54000, France
[g]Université Paris 7 Denis Diderot, UFR de Médecine, Paris F-75000, France
[h]Clinique Psychiatrique, CHRU Strasbourg, FTMS, Strasbourg, F-67000, France
[i]INSERM U1114, Physiopathologie et Psychopathologie Cognitive de la Schizophrénie, Hôpitaux Universitaires de Strasbourg, Strasbourg F-67000, France

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Abstract
Cannabis is one of the most prevalent drugs used worldwide. Regular cannabis use is associated with impairments in highly integrative cognitive functions such as memory, attention and executive functions. To date, the cerebral mechanisms of these deficits are still poorly understood. Studying the processing of visual information may offer an innovative and relevant approach to evaluate the cerebral impact of exogenous cannabinoids on the human brain. Furthermore, this knowledge is required to understand the impact of cannabis intake in everyday life, and especially in car drivers. Here we review the role of the endocannabinoids in the functioning of the visual system and the potential involvement of cannabis use in visual dysfunctions. This review describes the presence of the endocannabinoids in the critical stages of visual information processing, and their role in the modulation of visual neurotransmission

*Corresponding author at: Maison des Addictions, CHU Nancy, Hôpital St Julien, 1, rue Foller, Nancy F-54000, France. Tel.: +33 383858385; fax: +33 383852415.
E-mail address: v.laprevote@chu-nancy.fr (V. Laprevote).

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and visual synaptic plasticity, thereby enabling them to alter the transmission of the visual signal. We also review several induced visual changes, together with experimental dysfunctions reported in cannabis users. In the discussion, we consider these results in relation to the existing literature. We argue for more involvement of public health research in the study of visual function in cannabis users, especially because cannabis use is implicated in driving impairments.

1. Introduction

Cannabis use is very widespread in industrialized countries. In the United States, the lifetime prevalence of cannabis use is estimated at 42%, and the prevalence in the year preceding the interview at 21.5% (Degenhardt et al., 2008). In the European Union, some 75.5 million people aged 15–64 years old report having already smoked cannabis at least once in their lives, and 23 million Europeans used cannabis in the year preceding interview (European Monitoring Centre for Drugs and Drug Addiction, and Publications Office of the European Union, 2010). Regular cannabis use may have long-term health consequences. Part of these effects is comparable to that of tobacco, especially when smoked without a filter, such as bronchopulmonary cancers (Mehra et al., 2006), chronic respiratory diseases (Tetrault et al., 2007), arteritis (Sauvanier et al., 2002) and reproductive disorders (Holt et al., 2005; Vescovi et al., 1992). However, other outcomes are more directly linked to cannabis itself, such as psychiatric and cognitive effects. For example, higher risk of developing schizophrenia is correlated with cannabis use (Casadio et al., 2011; Moore et al., 2007). In a recent cohort study, 20 years of regular cannabis use was found to result in a significant intelligence quotient (IQ) decrease and major impairment in executive functions and processing speed (Meier et al., 2012). More specifically, the best-documented cognitive impairments due to regular cannabis use involve executive functions (Bolla et al., 2002; Pattij et al., 2008; Verdejo-García et al., 2006), memory (Bolla et al., 2002; Solowij and Battisti, 2008), and attention (Solowij et al., 1995). Studying the impact of cannabis use on these cognitive functions is particularly relevant from a clinical point of view. However, the precise neural mechanisms underlying impairments due to cannabis use, in particular those in cognitive functions critical for car driving, are still being debated. Consequently, modeling the effects of exogenous cannabinoids on the human brain on this basis is problematic because these high-level cognitive functions are tightly integrated and involve many brain areas (Aggleton, 2014; Funahashi and Andreau, 2013; Somers and Sheremata, 2013).

Low-level vision may therefore be a good candidate for conceptualizing the neural impact of regular cannabis use for several reasons. Despite the evolution of mammals, the visual function displays good preservation of functional and anatomical characteristics across species (Yoon et al., 2013), thus allowing the translation of findings between animals and humans. A broad range of techniques – electrophysiological, imaging and pharmacological – can be used alone or coupled to each other to study anatomical details and physiological or molecular mechanisms of the visual system (Disney et al., 2007; Katzner et al., 2011). For example, pharmacological modulation of gabaergic and glutamatergic receptors by the administration of agonists or antagonists may be useful techniques. In the human being, studying the earliest stages of visual processing, for example at the retina level, has the advantage of being less sensitive to attentional variation during experimental measurements, thus eliminating the bias of nonspecific generalized attentional deficit, which is difficult to control (Knight and Silverstein, 2001). Besides this fundamental question, and considering that the visual function seems to be altered in cannabis users, it is now crucial to obtain more insight on how cannabis use may change visual perception, especially given the pervasive role of vision in human everyday life. For example, cannabis users drive, and so we need to know whether or not regular intake of cannabis affects the visual ability of drivers.

This review looks at the involvement of the endocannabinoid system in visual processing, and whether exogenous cannabinoids may affect visual function. We review human and animal studies that have examined the distribution of cannabinoid receptors and ligands, together with those that have investigated the involvement of the cannabinoid system in neurotransmission and synaptic plasticity of visual information processing. We also review studies that have shown visual changes and experimental visual dysfunctions following both acute and chronic cannabis use. These results are discussed on the basis of the existing data in the literature. Since cannabis constitutes the most prevalent illicit drug implicated in road fatalities, we also argue for more involvement of public health research in the study of visual function among cannabis users (Hartman and Huestis, 2013).

2. Experimental procedures

A search for relevant articles was conducted in the Pubmed and Google Scholar databases using the following keywords (“CANNABIS” OR “CANNABINOID” OR “MARIJUANA” OR “THC”) AND (“VISION” OR “VISUAL PROCESSING” OR “VISUAL SYSTEM” OR “VISUAL CORTEX” OR “RETINAL PROCESSING” OR “RETINA” OR “THALAMUS”). All results up to February 28, 2014 were examined for the selection process. Relevant publications were chosen through an individual independent selection of titles by three authors (TS, VL, RS). The articles selected had to be written in English and be related to the topic of the review. Additionally, a manual search was performed on the bibliography of each selected article.

3. Cannabis and the endocannabinoid system

3.1. Main psychoactive components

The psychotropic effects of *Cannabis sativa* L. are mediated by two major compounds: Δ9-tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1964; Mechoulam et al., 1967) and cannabidiol (CBD) (Mechoulam and Shvo, 1963). The concentration of THC contained in cannabis consumed has been constantly increasing since the 1960s, raising the ratio of THC to CBD (Potter et al., 2008). THC may increase the risk of psychotic disorders in a specific high-risk population (Bossong and Niesink, 2010), whereas recent findings suggest that CBD may have antipsychotic properties (Schubart et al., 2014).

3.2. Receptors

Cannabinoid compounds are mainly active on CB1 and CB2 receptors (Devane et al., 1988; Herkenham et al., 1990; Howlett et al., 1986; Matsuda et al., 1990; Munro et al., 1993). CB1 receptors are predominantly expressed in the mammalian central nervous system (CNS), with a higher density in basal ganglia, hippocampus, cerebellum and cerebral cortices, correlated with the motor and cognitive regions of the brain (Glass et al., 1997; Herkenham et al., 1991, 1990; Hohmann and Herkenham, 1999; Mailleux et al., 1992; Moldrich and Wenger, 2000; Tsou et al., 1998; Westlake et al., 1994). CB2 receptors are mainly detected in the peripheral and immune tissues (Berdyshev, 2000; Munro et al., 1993; Sugiura and Waku, 2000; Wilson and Nicoll, 2001), but it appears that CB2 receptors also have a functional presence in the CNS at a lower level than CB1 receptors (Ashton et al., 2006; Gong et al., 2006; Lu et al., 2000; Onaivi et al., 2006, 2008; Ross et al., 2001; Van Sickle, 2005).

3.3. Main endocannabinoids

In mammals, two main compounds act on endocannabinoid receptors: *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Mechoulam and Hanus, 2000). Anandamide is involved post-synaptically through CB1 and CB2 receptors as a retrograde messenger to modulate the release of neurotransmitters (Egertová and Elphick, 2000; Glass and Northup, 1999), and expresses more affinity for CB1 than CB2 receptors (Felder et al., 1995). 2-AG acts pre-synaptically and has more affinity for CB1 receptors (Hanus et al., 2001; Marzo et al., 2004; Sugiura and Waku, 2000). Recent findings have shown that 2-AG is more readily detected in the brain than anandamide, and that it exerts less affinity for CB1 receptors than anandamide (Chevaleyre et al., 2006). In goldfish, anandamide and 2-AG appear to be expressed in all brain areas, with a higher level of anandamide in the hypothalamus and a higher level of 2-AG in the telencephalon (Valenti et al., 2005). In rats and humans, anandamide has been found in the cortex, hippocampus, striatum and cerebellum (Felder et al., 1995), correlated with higher levels of CB1 receptors, and in the thalamus, correlated with low levels of CB1 receptors (Egertová and Elphick, 2000; Felder et al., 1996).

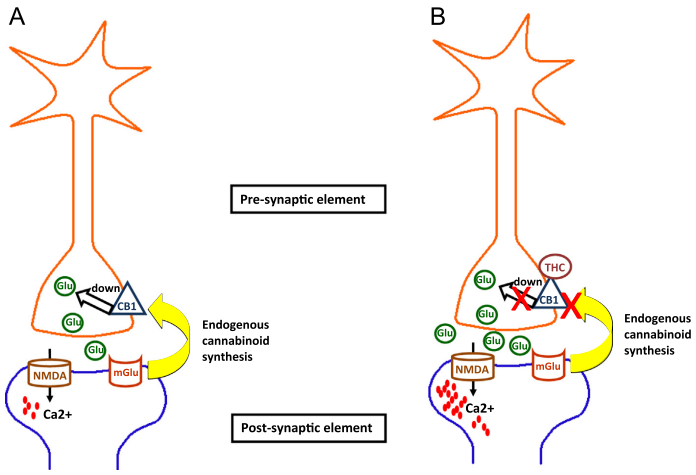

Figure 1 Role of the cannabinoid system in the regulation of neurotransmission in a glutamatergic synapse (A) and dysregulation induced by exogenous cannabinoids (B). (A) The synaptic release of glutamate (Glu) results in a post-synaptic influx of calcium (Ca^{2+}) through NMDA receptors (NMDA). The glutamate receptor (mGlu) is then stimulated, engaging a post-synaptic synthesis of endocannabinoids. Consequently, they regulate, through cannabinoid receptors CB1 (CB1), the synthesis and release of glutamate, thus preventing an increase in post-synaptic influx of Ca^{2+}. (B) The blockade of CB1 receptors by exogenous cannabinoids such as THC inhibits the pre-synaptic regulation of glutamate release, leading to an excess of post-synaptic influx of Ca^{2+}. This therefore induces apoptosis of the cell.

3.4. Synaptic process

CB1 receptors are detected at the level of pre-synaptic localization in the brain neurons (Mechoulam and Parker, 2013). They play a post-synaptic regulatory role by modulating the release of neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate (Mechoulam and Parker, 2013; Straiker and Mackie, 2006; Wilson and Nicoll, 2001). The stimulation of a glutamatergic neuron results in a synaptic release of glutamate, which induces a post-synaptic influx of calcium through NMDA receptors (Bossong and Niesink, 2010). The post-synaptic increase in the Ca^{2+} concentration activates the process of synaptic strengthening (Bossong and Niesink, 2010), and by stimulating the post-synaptic metabotropic glutamate receptor mGlu engages a post-synaptic synthesis of endocannabinoids. Through CB1 pre-synaptic receptors, endocannabinoids achieve a regulatory role on pre-synaptic glutamate release, which prevents an excessive post-synaptic release of calcium (Bossong and Niesink, 2010; Yazulla, 2008). Exogenous cannabinoids, such as THC, prevent the pre-synaptic regulation of glutamate release induced by endocannabinoids by blocking the cannabinoid CB1 receptor, and may lead to an excess of post-synaptic calcium influx, thus accelerating the pruning of the post-synaptic part of the synapse and the apoptosis of the cell (Bossong and Niesink, 2010; Yazulla, 2008). The role of the cannabinoid system in the synaptic process of a glutamatergic neuron is presented in Figure 1.

4. The endocannabinoid system and vision

Visual perception is a complex mechanism that embraces the cognitive processes for the retrieval of information from environmental light in order to construct a meaningful representation of the environment. Briefly, visual processing begins in the retina with the absorption of light by the photopigment of the photoreceptors, thus initiating the conversion of light into neural activity (Hoon et al., 2014). The retina also contains amacrine and horizontal cells acting as interneurons, and which join together bipolar and photoreceptor cells respectively, and Müller cells, which have a glial function (Hoon et al., 2014). The visual information is relayed to the brain by the optic nerve formed by the axons of the ganglion cells (Hoon et al., 2014). The first main relay in the brain's visual pathways is in the thalamus, where the lateral geniculate nucleus performs differential processing of contrast, spatial distribution and temporal sequence (Tootell et al., 1988). The information is then transmitted to the occipital cortex, especially in the primary and secondary visual cortex, which provides knowledge about forms, movements or colors (Livingstone and Hubel, 1988). From there, the ventral pathway goes to the frontal lobe through the temporal lobe, while the dorsal pathway goes to the frontal lobe through the parietal lobe. These two pathways perform differential processing, allowing the identification and localization of the information, and help to form a coherent, complex representation of the environment (Livingstone and Hubel, 1988). All the areas briefly presented here are densely interconnected, allowing retroactive complex interactions (Nowak et al., 1997). Analysis of the literature on cannabis and vision yields information on three main stages in this visual processing that are of interest because of their critical role and their accessibility for measurement: retina, thalamus and visual cortex.

4.1. Retinal localization

Animal studies have shown that cannabinoid CB1 and CB2 receptors are expressed in the retina of several species. CB1 and CB2 receptors are detected in the retina of goldfish (Cottone et al., 2013; Straiker et al., 1999a; Yazulla et al., 2000), rodents (Buckley et al., 1998; Cecyre et al., 2013; Lalonde et al., 2006; López et al., 2011; Lu et al., 2000; Porcella et al., 1998; Straiker et al., 1999a; Zabouri et al., 2011) and non-human primates (NHP) (Bouskila et al., 2012, 2013; Straiker et al., 1999a). CB1 receptors are found in the retina of the chick and the tiger salamander (Straiker et al., 1999a).

In addition, CB1 and CB2 receptors are expressed in the human retina. CB1 receptors are detected in the human retina in the inner plexiform layer (IPL), outer plexiform layer (OPL), two synaptic layers of the retina, inner nuclear layer, ganglion cell layers, outer segments of photoreceptor cells and retinal pigmentary epithelium (RPE) cells (Porcella et al., 2000; Straiker et al., 1999b; Wei et al., 2009). CB2 receptors are expressed in the human RPE cells (Wei et al., 2009). Recent findings suggest that the deletion of CB1 receptors in the human RPE may protect RPE cells from oxidative damage, the key mechanism of age-related macular degeneration (AMD) (Wei et al., 2013). This suggests a possible modulation of information transmission by the cannabinoid system at the retina level.

2-AG and anandamide, two major ligands of CB1 and CB2 receptors, have also been detected in the retina. In animal species, 2-AG and anandamide are expressed in rat and bovine retina (Bisogno et al., 1999; Straiker et al., 1999a), while anandamide is found in goldfish, porcine and bovine retina (Bisogno et al., 1999; Glaser et al., 2005; Matsuda et al., 1997). In humans, 2-AG is expressed at a high level in the retina (Chen et al., 2005; Matias et al., 2006), whereas anandamide is detected at a lower level in the retina (Chen et al., 2005; Matias et al., 2006; Stamer et al., 2001). Interestingly, a recent study showed that their concentrations might be changed in diabetic retinopathy (DR) and AMD (Matias et al., 2006), also showing a possible involvement of cannabinoid ligands in the retinal pathologic processes.

The retina constitutes the best documented level of visual information processing concerning the regulatory role of the cannabinoid system. A number of animal studies have highlighted the involvement of the cannabinoid system in the synaptic process, thus allowing the modulation of the neurotransmission at the retina level. First, the cannabinoid system is involved in the regulation of several inward and outward ionic channels. For instance, cannabinoid agonists induce a dose-dependent reversible modulation of calcium, potassium and chloride currents in bipolar, rod, cone and ganglion cells (Fan and Yazulla, 2003, 2004, 2005, 2007; Lalonde et al., 2006; Opere et al., 2006; Straiker et al., 1999a; Straiker and Sullivan, 2003; Yazulla et al., 2000; Zhang et al., 2013). Additionally, THC may inhibit the

monoamine oxidase activity in the retina, thus regulating the level of neurotransmitters (Gawienowski et al., 1982). Also, cannabinoid agonists alter the spontaneous post-synaptic currents within retinal ganglion cells (Middleton and Protti, 2011). Finally, by acting on ionic currents and electrical potentials, the cannabinoid system may modulate the release of several neurotransmitters such as dopamine, noradrenaline, GABA, and glutamate (Middleton and Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Straiker and Sullivan, 2003; Weber and Schlicker, 2001). By their likely involvement in the retinal neurotransmission, cannabinoid agonists affect phototransduction, leading to alterations in the retinal sensitivity, which was studied using whole-cell patch-clamp recordings performed from ON-bipolar cells and cones (Fan and Yazulla, 2005; Struik et al., 2006; Yazulla et al., 2000). Interestingly, such involvement of the cannabinoid system in the modulation of the retinal response has been confirmed by ERG measurements. The retinal function may be assessed by several ERGs using different stimulations. Flash ERG measurements allow the assessment of the functional properties of the photoreceptors and bipolar–Müller cell complex following a flash stimulation. Pattern ERG evaluates the macular and ganglion cell functions in response to a reversible black and white checkerboard, and multifocal ERG explores the spatial characteristics of central retinal cone function in response to multiple hexagons distributed over a screen (Holder et al., 2010). Using fERG under both scotopic and photopic conditions, mice lacking CB1 or CB2 receptors presented modifications of a-wave and b-wave amplitudes (Cecyre et al., 2013). These waves respectively represent an electronegative component generated by the photoreceptors and an electropositive component originating from bipolar cells and Müller cells.

Besides, Chaves et al. (2008) have shown the involvement of the cannabinoid system in plasticity mechanisms occurring between the retina and the thalamus. Using immunohistochemistry, immunoblotting, and real-time PCR techniques, they have demonstrated that retinal ablation increases the level of CB1 protein in the controlateral optic tectum in the adult chick brain. These findings suggest that the cannabinoid system participates in the neuroprotection of the visual function and plays a major role in development, through synaptic plasticity, of the visual system. Such functions may therefore be disrupted by exogenous cannabinoids.

Based on these findings, the cannabinoid system may modulate the human visual function at the retina level by its involvement in the retinal transmission of the visual signal (Laprevote et al., 2015). Since alterations at the central level in dopamine and serotonine neurotransmission may affect the ERG measurements and thus alter the retinal response, the retinal function may constitute a possible biological marker of brain neurochemistry (Lavoie et al., 2014).

4.2. Thalamus localization

CB1 receptors are heterogeneously distributed in the thalamus in rats (Herkenham et al., 1990, 1991; Moldrich and Wenger, 2000; Tsou et al., 1998), mice (Yoneda et al., 2013), NHP (Herkenham et al., 1990; Yoneda et al., 2013), and humans (Glass et al., 1997; Herkenham et al., 1990). Interestingly, CB1 receptors are detected in the lateral geniculate nucleus (LGN), the colliculus superior and the suprachiasmatic nucleus in the rat and mouse (Herkenham et al., 1991; Yoneda et al., 2013), and in the LGN and the colliculus superior in humans (Glass et al., 1997). Both the LGN and the colliculus superior have neural connections with the primary visual brain area, and relay visual information from the retina to the primary visual cortex (Sherman and Guillery, 2002).

Dasilva et al. (2012) have shown that the administration of cannabinoid agonists induces an excitatory effect on a part of cells and an inhibitory effect on another part of the cells in the LGN of adult rats, thus revealing two cell populations. These effects were mediated by the activation of CB1 receptors, and were blocked by a cannabinoid antagonist. As a consequence, both spontaneous and visual activities of the cells were altered. According to these findings, cannabinoid agonists, through CB1 receptors, may modulate, at a cellular level, the visual neurotransmission from the thalamus to the visual cortex. This demonstrates the potential ability of cannabis to disrupt the processing of visual information at the thalamic level.

4.3. Cortical localization

The visual cortex forms a later stage in visual information processing. CB1 and CB2 receptors are detected in the primary (V1) and secondary (V2) visual cortex of rats and mice (Gong et al., 2006; Herkenham et al., 1991; Onaivi et al., 2006; Tsou et al., 1998; Yoneda et al., 2013). In NHP, CB1 receptors have also been found in V1 and V2 (Ong and Mackie, 1999). Interestingly, CB1 receptors are more strongly expressed in V2 (layers I, II, IV, V, VI) than in V1 (layers I, II, III, IVA, IVB, IVC, V, VI) in humans (Glass et al., 1997).

Like in the retina and the LGN, the cannabinoid system is able to modulate the neural transmission in the adult visual cortex. Interestingly, Ohiorhenuan et al. (2014) have recorded the electroencephalogram (EEG), local field potentials (LFP) and single-unit activity of V1 and V2 in adult NHP. A decrease in EEG power, LFP power and LFP coherence was induced by the administration of a cannabinoid agonist. Additionally, at the level of individual neurons they found an increase in the latency and duration of the neuronal response. Taken together, these findings show the involvement of the cannabinoid system in the modulation of the neuronal activity of the visual cortex at the level of individual neurons as well as at the level of neuronal networks.

Besides, the developmental role of the cannabinoid system during early postnatal development in visual cortical plasticity has been recently established in animal studies. This knowledge warrants attention because it may inform us on the potential effects of cannabis use during pregnancy. In mice aged from postnatal day 13 (P13) to P27, the administration of a cannabinoid agonist significantly reduced both the amplitude and the frequency of inhibitory post-synaptic currents (IPSC) in layer IV of V1 (Garkun and Maffei, 2014). Using the ocular dominance plasticity, a model of cortical plasticity Liu et al. (2008) found that during

Table 1 Summary of cannabinoid functions in critical stages of visual processing.

Visual structures	Functions of cannabinoids	Species	References
Retina	Ionic channels	Tiger salamander	Straiker et al. (1999a), Straiker and Sullivan (2003)
		Goldfish	Fan and Yazulla (2003, 2004, 2005, 2007), Yazulla et al. (2000)
		Rat	Lalonde et al. (2006), Zhang et al. (2013)
		Bovine	Opere et al. (2006)
	Enzymatic activity	Bovine	Gawienowski et al. (1982)
	Release of neurotransmitters	Tiger salamander	Straiker and Sullivan (2003)
		Guinea-pig	Schlicker et al. (1996), Weber and Schlicker (2001)
		Mouse	Middleton and Protti (2011)
		Bovine	Opere et al. (2006)
	Synaptic plasticity	Chick	Chaves et al. (2008)
	Retinal sensitivity	Goldfish	Fan and Yazulla (2005), Struik et al. (2006), Yazulla et al. (2000)
	Functioning of photoreceptors and bipolar–Müller cells	Mouse	Cecyre et al. (2013)
	Oxidative damage	Human	Wei et al. (2013)
Thalamus	Neurotransmission	Rat	Dasilva et al. (2012)
Cortex	Neurotransmission	Non-human primate	Ohiorhenuan et al. (2014)
	Synaptic plasticity	Mouse	Garkun and Maffei (2014), Liu et al. (2008), Huang et al. (2008), Jiang et al. (2010a, 2010b)

postnatal development, the blockade of cannabinoid receptors prevented the ocular dominance shift in layer II/III, but not in layer IV. As observed in long-term depression (LTD), cannabinoid ligands are involved in the heterosynaptic LTD (hetero-LTD) of excitatory synapses, which is predominant from P7 to P14 (Crozier et al., 2007; Huang et al., 2008). Finally, the cannabinoid system plays a major role in the maturation of GABAergic transmission between eye opening and puberty (Jiang et al., 2010a, 2010b).

The endocannabinoid system is detected through the critical stages of visual information processing. As this system is involved in neural transmission and synaptic plasticity in the visual cortex, exogenous cannabinoids may lead to impairment of the visual function. The main functions of cannabinoids in these crucial stages of visual processing are summarized in Table 1.

5. Cannabis use and human vision

5.1. Case reports and case series

Several publications have related that acute use of cannabis results in improved visual function and contributes to visual side-effects. The most surprising report concerns Jamaican fishermen, whose night vision improved shortly after smoking *C. sativa*, and who were able to navigate safely through coral reefs in night conditions (West, 1991). This observation was recently confirmed by showing that the administration of dronabinol, a synthetic THC, resulted in a dose-related increase in scotopic sensitivity, and that inhaling a mixture of *C. sativa* and tobacco resulted in an enhanced dark adaptation and scotopic sensitivity (Russo et al., 2004). In both situations, vision was improved. Furthermore, Consroe et al. (1997) report that patients with multiple sclerosis used cannabis to reduce some of their symptoms including visual symptoms such as double vision or vision dimness. On the other hand, a study conducted nearly four decades ago, which examined the analgesic effect of THC, found that single oral dose administration of THC induced visual side-effects such as blurred vision (Noyes et al., 1975). Interestingly, all these effects are acute consequences of cannabis use.

Besides these acute visual changes, several case series have described residual visual effects of regular cannabis use. A case report describes the occurrence of flickering black spots in a man after cessation of five years of daily cannabis use, and persisting for 8 months after drug abstinence (Laffi and Safran, 1993). Similarly, a case series reported several visual disturbances (visual distortions, illusions of movement, color vision disturbances, flashbacks) in eight regular cannabis smokers, which persisted after cessation of use (Lerner et al., 2011). These findings showing the involvement of cannabinoid use in visual abnormalities are isolated, and only one study, to our knowledge, has studied the impact of chronic cannabis use on a large number of visual parameters compared with a non-user group (Dawson et al., 1977). In this large study, only small differences were measured concerning Snellen acuity, intra-ocular pressure, pupil response and color vision. Unfortunately, contrast sensitivity was not evaluated in cannabis users in this study.

5.2. Experimental studies

Despite these clinical presumptions, few studies have evaluated the earliest stages of visual processing in cannabis users. Even so, experimental tests of the visual function have shown several impairments. For example, regular cannabis users have increased foveal glare recovery time after smoking a cigarette containing 8 or 15 mg of THC (Adams et al., 1978). This might demonstrate a possible direct acute action of THC on retinal processing. Ehrenreich et al. (1999) have shown that the use of cannabis between ages 12 and 16 years was associated with impairments in visual scanning in adulthood. Similarly, chronic cannabis users with early age drug consumption have shown longer response times and a higher number of fixations on a square stimulus than controls in a visual scanning task (Huestegge et al., 2002), and both are residual effects of cannabis use. In a study assessing the residual impact of regular cannabis use on visuomotor integration, the authors showed that cannabis affected the strength of the binding between task-relevant stimulus and response features (Colzato and Hommel, 2008). This suggests a critical role of dopaminergic transmission, in particular through CB1 receptors, in visuomotor integration, which may be modulated by cannabinoids. Binocular depth inversion (BDI) is an illusion of visual perception informative of impaired visual processing. It is sensitive and regularly used in psychiatric and addictive disorders such as psychotic states and alcohol withdrawal (Emrich, 1989; Schneider et al., 1998, 2002). Both acute and chronic cannabis use may induce a reduction of BDI, showing acute and residual effects of cannabis, respectively (Emrich et al., 1991; Leweke et al., 1999; Semple et al., 2003).

A few studies using cerebral imaging have investigated the consequences of cannabis use on brain areas involved in visual processing. A radial visual checkerboard in alterning block viewed during functional magnetic resonance imaging (fMRI) was used to assess the acute impact of 10 mg of THC and 600 mg of CBD compared with placebo on visual processing in healthy volunteers (Winton-Brown et al., 2011). THC decreased activation in the secondary visual cortex, which was activated in the placebo condition, and increased activation in the primary visual cortex in the right hemisphere, compared with placebo. Also, CBD increased activation in the right occipital lobe compared with placebo. Interestingly, during visual processing, THC and CBD have similar effects on brain response in several regions and opposite effects in others. Additionally, in MRI, an interesting study has reported as a residual consequence of cannabis use a significant reduction in global and bilateral thalamic volume in cannabis users compared with a non-user group in a population at high familial risk of developing schizophrenia (Welch et al., 2011). Since the thalamus relays the visual information between the retinal and cortical pathways, and has neural connections with the retina and the primary visual cortex, the loss of thalamic volume due to cannabis use may have potential consequences on the processing of visual information.

Several studies performing visually evoked potential measurements in cannabis users have shown inconsistent results, in particular for the P300 component. This is a positive wave that represents the amount of attentional resources involved in stimulus characterization (Polich, 2007). For example, cannabis users showed a reduction in the amplitude of the visual P300 compared with non-users when all subjects were psychiatric inpatients. However, when users and non-users were screened to be healthy participants, no difference was seen (Patrick et al., 1995). In this situation, psychiatric disorders and drugs could disturb the results. In addition, in an older study that evaluated the consequences of the inhalation of THC on many cardiovascular, respiratory and neurological parameters, no difference was shown on visually evoked potentials (Low et al., 1973). More recently, visually event-related potentials recorded 2 h after acute intakes of different THC doses during a visual selective attention task showed a dose effect on several parameters (Böcker et al., 2010). A significant acute dose effect on the amplitude of P300 and SFD 80, which is related to perception of high versus low spatial frequency gratings, was observed. This suggests a non-selective decrease in attentional or processing resources. Evaluation of steady-state visually evoked potential (SSVEP), which represents a type of EEG response of visual occipital brain areas to periodic visual stimulation, has shown residual effects of cannabis, such as impairments in SSVEP and transient N160 component in cannabis users (Skosnik et al., 2006). The transient N160 component is a negative component representing a main stage of processing in the recognition and extraction of a visual pattern (Simon et al., 2007). Interestingly, female cannabis users and cannabis users with early age drug consumption showed decreased power values at 18 Hz in SSVEP. Additionally, the transient N160 component appears to be reduced in cannabis users. Based on these findings, cannabis use may affect both early and later cortical stages of visual information processing.

These impairments in visual processing are correlated with previous clinical observations. In both situations, cannabis use is implicated in clinical and electrophysiological visual dysfunctions. As cannabis use is implicated in visual dysfunctions, the impact of regular cannabis use on visual information processing warrants evaluation for its consequences on public health.

6. Discussion

This review examines the broad involvement of the cannabinoid system in visual processing, and the potential consequences of regular cannabis use. The cannabinoid system is closely involved in the visual function for several reasons. Endocannabinoids are expressed through critical stages of the visual system, such as in the retina, the LGN and the visual cortex. The modulation of the cannabinoid system by exogenous agonists or antagonists may disrupt the neural transmission in the retina, the thalamus and the visual cortex, thereby modifying the processing of the visual information. In the longer term, the endocannabinoid system may play a dynamic role in the development and function of the visual system through synaptic plasticity.

Besides the potential role of the cannabinoid system on the early processing of visual information, there is still a lack of knowledge about the potential effect of regular cannabis use on the human visual function. Nonetheless, acute and regular cannabis uses are correlated with alterations of human vision. Interestingly, case reports and case

series have shown that cannabis use can lead to visual disturbances, reduction of visual symptoms and improvement of the visual function. Furthermore, experimental studies have reported several dysfunctions at the retina and cortical level in visual information processing of cannabis users. Based on these findings, we need more studies, for example clinical prospective studies in cannabis users versus healthy controls, that evaluate visual information processing in cannabis users in order to find out whether cannabis use disturbs visual function. Such information is critical and constitutes a major public health challenge, since cannabis is one of the most prevalent drugs detected in drivers' blood or oral fluid, and is implicated in motor vehicle accidents (MVAs) (Hartman and Huestis, 2013). The association between cannabis and driving impairments has been clearly established in the United States and the European Union (Hartman and Huestis, 2013; Raes and Verstraete, 2006). For example, driving under the influence of cannabis is correlated with increased crash risk and decreased driving ability (Hartman and Huestis, 2013). Car drivers classified as positive for cannabis therefore represent an expanding target audience for prevention campaigns in public healthcare provision. A better knowledge of the impact of cannabis on cognitive functions critical for driving is therefore crucial, especially for the decrease in mortality and morbidity on roads and for the development of appropriate legislation. Further investigation to evaluate the visual function in regular cannabis users and to assess the impact on regular cannabis use on driving is needed.

On this basis, studying the visual function in regular cannabis users represents a relevant and original approach allowing the evaluation of the impact of exogenous cannabinoids on an accessible, well-studied function (Palczewski, 2011). Currently, mounting evidence suggests that visual processing represents an additional interesting measure to explore neural dysfunctions associated with mental disorders (Javitt, 2009; Yoon et al., 2013). The visual system forms one of the early information processing entities, and has now been largely studied (Palczewski, 2011). Much technological progress has been recently made in the study of structural and functional characteristics of the visual system (Disney et al., 2007; Katzner et al., 2011; Palczewski, 2011), such as the development of non-invasive methods yielding valuable information on the central level of neurotransmitter, for example magnetic resonance spectroscopy (MRS). Additionally, there are standardized measures to examine different stages of visual processing. Concerning the retina, standard clinical electroretinography allows the evaluation of the retinal function in dark and light adaptation to differentiate the rod and cone responses (Marmor et al., 2009). Scotopic ERG evaluates the rod response and the response of the ON-bipolar cells, while photopic ERG evaluates cone response and simultaneous ON and OFF pathways (Holder et al., 2010). The contrast sensitivity function assesses spatial specificity, and temporal discrimination of the visual system is evaluated by both visual backward masking (Giersch and Herzog, 2004) and simultaneity threshold measurements (Brown et al., 2003). These behavioral measurements can be extended by electrophysiological ones such as event-related potentials (ERP) to evaluate temporal dynamics of early visual processing. Cerebral imaging coupled with the previous behavioral paradigms then allows the evaluation of the cerebral areas involved in visual information processing.

There are many possible reasons for the difficulties met in developing clinical studies assessing the impact of cannabis consumption (Carlin et al., 1972; Weil et al., 1969). Firstly, because cannabis is an illicit drug in most countries, cannabis users may be suspicious and reluctant to participate in a clinical study. They may think that the main goal of studying cannabis is to prove its toxic effects and thus plead against its legalization. Secondly, it is important to control composition and route of administration to limit some variations in measurements. Cannabinoid agonists may be administrated by oral, intra-venous or inhaled routes, and this may change the dose ingested. Similarly, the frequency and extent of use may vary with the type of drug (Huestis, 2007). Furthermore, the evolution of the concentration of THC and CBD contained in the cannabis consumed complicates the understanding of dose-related effects of each compound. Thirdly, the acute administration of cannabis induces impairments in cognitive functions (Crean et al., 2011; Lundqvist, 2005; Solowij and Battisti, 2008), making it difficult to perform any kind of measurement, and especially to interpret the results. Fourthly, cannabis may be associated with other psychoactive drugs, complicating the extraction of the specific effect of cannabis use (González Pérez et al., 1995). A number of studies that have evaluated the cognitive functions in cannabis users have already overcome these various difficulties. Consequently, it is critical to obtain data regarding the impact of cannabis intake on the visual function in regular users.

Several methodological considerations have to be borne in mind for future research on cannabis. One is to accurately evaluate, with a consistent measurement tool, the dose of cannabinoids consumed to seek a dose–effect relationship. Also, cannabis may induce acute, residual or withdrawal effects that can be evaluated and so reported to provide a clear picture of the consequences of cannabis use. In studies assessing the residual effects of cannabis, measurements must be performed some time after the last cannabis use to prevent acute cognitive deficits such as attentional and awareness disturbance (Knight and Silverstein, 2001). The use of licit or illicit drugs associated with cannabis use makes screening for these drugs necessary, as they are liable to disrupt the functioning of several biological systems, for example thiamine deficiency in alcohol use, thus altering the cannabinoid function. In future studies, urine analyses should therefore be systematically performed to rule out these confounding factors. Some substances such as tobacco or alcohol may also be evaluated by questionnaires. Finally, since cannabis is widely used with tobacco, for example smoked as a mixture (Agrawal et al., 2012), a control group of tobacco users may be needed to differentiate the effects of each drug.

Developing new models and biomarkers assessing the neurotoxicity of substance consumption and allowing the early detection of these disorders now represents a new challenge in the neurosciences. For example in schizophrenia, the development of tasks that allow the evaluation of visual perception has been added to the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) battery (Carter et al., 2011). Thus further work is needed to develop valid, reproducible,

reliable and easy-to-use markers of neural activity in cannabis users, thereby facilitating the screening of these disorders and the understanding of neural mechanisms underlying related deficits. Visual function may provide some of these markers.

7. Conclusion

Although visual abnormalities have been observed in cannabis users, few studies have yet evaluated the impact of cannabis use on visual information processing. Recent findings in animal and human studies have shown the distribution of endocannabinoids throughout the visual system and their involvement in critical mechanisms such as visual synaptic plasticity and visual neurotransmission. Such knowledge may enhance our understanding of the biological mechanisms underlying cannabis-related deficits, and so prompt more studies in cannabis users. Additionally, technological advances such as the development of precise, non-invasive measurement, together with standardized protocols, currently allow the rigorous assessment of visual function and ensure reproducible results. Consequently, further investigation of the visual function at the retinal and cortical levels after both acute and chronic cannabis use is needed to provide a clearer picture of visual dysfunctions due to cannabis use. We see that studying the effects of cannabis use is far from straightforward. This review outlines some methodological considerations that may help future research on this public health issue.

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Contributors

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Conflict of interest

All the authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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JAMA Ophthalmology | Original Investigation

Association Between Regular Cannabis Use and Ganglion Cell Dysfunction

Thomas Schwitzer, MD; Raymund Schwan, MD, PhD; Eliane Albuisson, MD, PhD; Anne Giersch, MD, PhD; Laurence Lalanne, MD, PhD; Karine Angioi-Duprez, MD, PhD; Vincent Laprevote, MD, PhD

IMPORTANCE Because cannabis use is a major public health concern and cannabis is known to act on central neurotransmission, studying the retinal ganglion cells in individuals who regularly use cannabis is of interest.

OBJECTIVE To determine whether the regular use of cannabis could alter the function of retinal ganglion cells in humans.

DESIGN, SETTING, AND PARTICIPANTS For this case-control study, individuals who regularly use cannabis, as well as healthy controls, were recruited, and data were collected from February 11 to October 28, 2014. Retinal function was used as a direct marker of brain neurotransmission abnormalities in complex mental phenomena.

MAIN OUTCOMES AND MEASURES Amplitude and implicit time of the N95 wave on results of pattern electroretinography.

RESULTS Twenty-eight of the 52 participants were regular cannabis users (24 men and 4 women; median age, 22 years [95% CI, 21-24 years]), and the remaining 24 were controls (20 men and 4 women; median age, 24 years [95% CI, 23-27 years]). There was no difference between groups in terms of age ($P = .13$) or sex ($P = .81$). After adjustment for the number of years of education and alcohol use, there was a significant increase for cannabis users of the N95 implicit time on results of pattern electroretinography (median, 98.6 milliseconds [95% CI, 93.4-99.5]) compared with controls (median, 88.4 milliseconds [95% CI, 85.0-91.1]), with 8.4 milliseconds as the median of the differences (95% CI, 4.9-11.5; $P < .001$, Wald logistic regression). A receiver operating characteristic curve analysis (area under the curve, 0.84 [95% CI, 0.73-0.95]; $P < .001$) revealed, for a cutoff value of 91.13 milliseconds, a sensitivity of 78.6% (95% CI, 60.5%-89.8%) and a specificity of 75.0% (95% CI, 55.1%-88.0%) for correctly classifying both cannabis users and controls in their corresponding group. The positive predictive value was 78.6% (95% CI, 60.5%-89.8%), and the negative predictive value was 75.0% (95% CI, 55.1%-88.0%).

CONCLUSIONS AND RELEVANCE Our results demonstrate a delay in transmission of action potentials by the ganglion cells in regular cannabis users, which could support alterations in vision. Our findings may be important from a public health perspective since they could highlight the neurotoxic effects of cannabis use on the central nervous system as a result of how it affects retinal processing.

Invited Commentary

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Vincent Laprevote, MD, PhD, Pôle Hospitalo-Universitaire de Psychiatrie du Grand Nancy, Centre Psychothérapique de Nancy, 1, rue du Docteur Archambault, Laxou F-54 521, France (vincent.laprevote@cpn-laxou.com).

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The retina is an easy-to-access anatomic and developmental extension of the central nervous system,[1] which several research teams have suggested as being a crucial site for investigating human central synaptic transmission in complex mental phenomena.[2-12] Among these phenomena, the increasing use of cannabis represents an ever-growing public health challenge,[13] but little is known about the effect of cannabis use on human neural synaptic transmission. Retinal processing could constitute a breakthrough on this issue.

This study aimed to assess the stage of the retinal ganglion cells (RGCs) because it is particularly relevant to study the effect of regular cannabis use on human neural synaptic transmission. Retinal ganglion cells are the last and most integrated stage of retinal processing and the first retinal stage providing visual information in the form of action potentials, such as is found in the brain.[14] The endocannabinoid system is detected in RGCs and is involved in RGC synaptic transmission.[3,5,15] For example, in animals, cannabinoid agonists reduce glutamate release in rodent RGCs.[16,17] In humans, glutamate is also a main transmitter involved in retinal physiologic structure and in the vertical transmission of retinal information.[18,19] The action of cannabis on central glutamatergic transmission[20] may thus disturb RGC function in humans. To verify this hypothesis, we used a standard electrophysiological measurement called pattern electroretinography (PERG),[21] which involved averaging a high number of responses, thereby ensuring reproducibility of the results.[22] With PERG, the best marker of RGC function is a negative wave—the N95 wave—2 parameters of which are usually known as the amplitude and the implicit time, which denotes the time needed to reach the maximal amplitude of N95.[21,22]

We describe the results of the first study, to our knowledge, to assess the effect of regular cannabis use on human RGC function. Given the role of the cannabinoid system in regulating RGC synaptic transmission, we hypothesized that the RGC response can be affected by regular cannabis use.

Key Points

Question What is the effect of regular cannabis use on the function of retinal ganglion cells?

Findings In this case-control study of 28 individuals who regularly used cannabis and 24 controls, a large delay in retinal information processing was found in regular cannabis users compared with controls based on an increase in N95 implicit time on results of pattern electroretinography.

Meaning Although this study is preliminary and not designed to determine cause and effect, the findings suggest that retinal function might be used as a marker of brain neurotransmission abnormalities in cannabis users.

Methods

Study Population

Twenty-eight individuals who regularly used cannabis and 24 matched, healthy, drug-naive controls were recruited among the general population via a special press campaign, and data were collected from February 11 to October 28, 2014. Before taking part in the study, volunteers provided their detailed psychoactive drug and medical history, underwent a full psychiatric evaluation, and signed consent forms detailing all aspects of the research. All participants received payment in the form of €100 (approximately US $110) in gift vouchers. The study protocol met the requirements of the Declaration of Helsinki[23] and was approved by the Nancy University Hospital Ethics Committee. This study is part of a larger project, Causa Map, which is researching the effect of regular cannabis use on the visual system. All participants also underwent neuropsychological assessments and electroencephalography while they performed several visual tasks. Given the innovative nature of these measurements, the protocol provides an intermediate analysis that is focused on RGC functioning.

The inclusion criteria for the cannabis group were regular cannabis use at the rate of at least 7 cannabis consumptions per week during the past month, positive results for tetrahydrocannabinol metabolites on a urine toxicology test, no other illicit substance use in the past month, negative results for other illicit substances on a urine toxicology test, and no *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of Axis I disorders. Since tobacco is regularly mixed with cannabis in cigarettes (joints), cannabis users may meet the criteria for tobacco dependence according to the Fagerström test. Cannabis users were required to present with at least 12 hours of abstinence of cannabis use so that there were no acute cognitive dysfunctions owing to cannabis use.

Inclusion criteria for the healthy controls were no history of illicit substance use, negative results for tetrahydrocannabinol metabolites and other illicit drugs on a urine toxicology test, and no history of *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnosis of Axis I psychiatric disorders. All participants were aged 18 to 35 years, had no history of neurologic disease, no family history of schizophrenia or bipolar disorders, and were not taking medication except for oral contraceptives in the case of women. They had no history of ophthalmologic disease except for corrected refractive errors. All participants had normal results on ophthalmic evaluation, which included visual acuity and a fundoscopic examination. More important, visual acuity measured with the Monoyer Scale was at least 10/10 in each eye for all participants. None of the participants reported visual symptoms, and none was found to have any media opacities. If participants reported alcohol dependence according to their score in the Alcohol Use Disorders Identification Test (AUDIT), they were excluded from the study.

Clinical and Biological Assessments

The Mini-International Neuropsychiatric Interview was administered to assess current and past history of psychiatric diseases and substance use. In addition, the Cannabis Abuse Screening Test, Fagerström Test, and AUDIT were performed to assess use, abuse, or dependence with respect to cannabis, tobacco, and alcohol, respectively. The extent of cannabis use

Table. Demographic and Substance Use Characteristics of the Participants

Characteristic	Value[a]	
	Cannabis Users (n = 28)	Controls (n = 24)
Male, No. (%) [95% CI]	24 (86) [69-94]	20 (83) [64-93]
Age, y	22 (21-24)	24 (23-27)
Education, y	13.5 (13-14)	15 (14-16)
No. of alcohol uses per week	4 (3-6)	1 (0-2)
Alcohol Use Disorders Identification Test score	6 (4-10)	3 (1-4)
Fagerström Test score (n = 26)	1 (0-2)	NA
No. of cigarettes per day	3.5 (2-6)	NA
Age of first cannabis use, y	16 (16-17)	NA
Total years of cannabis use	6 (5-12)	NA
No. of joints per week	20 (14-21)	NA
Cannabis Abuse Screening Test score	4 (3-5)	NA
No. of grams of cannabis per week	5 (3-6)	NA

Abbreviation: NA, not applicable.

[a] Data are presented as median (95% CI) unless otherwise indicated.

was clinically assessed in an interview and a questionnaire as follows: age when regular cannabis use began, total years of cannabis use, average number of joints smoked daily and weekly during the past month, and average number of grams of cannabis smoked weekly (**Table**). To obtain objective confirmation of cannabis consumption, urine drug tests (nal von minden) were performed for cannabis, buprenorphine, benzodiazepines, cocaine, opiates, amphetamines, and methadone immediately before PERG testing.

PERG Measurements

Pattern electroretinography measurements were compiled according to the International Society for Clinical Electrophysiology of Vision standards for PERG.[21] The MonPackOne system (Metrovision) was used for stimulation, recording, and analysis. Electrical signals were recorded simultaneously from both eyes (averaged for analysis) on nondilated pupils, with Dawson-Trick-Litzkow electrodes (Metrovision) placed at the bottom of the conjunctival sac. Ground and reference electrodes were attached to the participant's forehead and external canthi. A black-and-white reversible checkerboard was used, with 0.8° check size, 93.3% contrast level, 100 candela/m^2 constant luminance white area, and 4 reversals per second. The participant was positioned 1 m from the screen. In the case of participants with refractive disorders, an appropriate optic correction was provided. At least 220 responses were recorded for each participant, with constant ambient room lighting to achieve the best signal to noise ratio. Pattern electroretinography data were analyzed with Moniteur Ophthalmique (Metrovision). Pattern electroretinography analysis was performed with the experimenter masked to the status of the participant being recorded (ie, cannabis user or control). Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. The electronegative component (N95) is attributed to the RGC and reflects their response.[21] Two main parameters are derived from N95, known by convention as the amplitude measured in microvolts and the implicit time measured in milliseconds. The N95 amplitude is measured from the trough of the N95 wave to the peak of the P50 wave. Implicit time denotes the time taken to reach the maximum N95 amplitude.

Statistical Analysis

Depending on the nonparametric distribution of several variables included in the analyses, the Mann-Whitney test, χ^2 test, and Spearman rank correlation test were used when appropriate to compare the 2 groups or to test the association between variables. Among all the variables and in this particular context, the relevant differences between the 2 groups involved N95 implicit time, years of education, AUDIT score, and average number of alcohol uses per week. To analyze N95 implicit time between the two groups, we used logistic regression to adjust for years of education and alcohol use. As average alcohol use per week was correlated with the AUDIT score, we kept the AUDIT score in the analysis. The logistic regression included N95 implicit time, years of education, and the AUDIT score, with cannabis users and controls as the binary outcome variable. A receiver operating characteristic curve was applied to the N95 implicit time values to estimate the sensitivity and specificity of cutoff values between regular cannabis users and controls. Since this study is a pilot study based on preliminary data, we chose to use a conservative level of significance in comparison with α<.025. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp).

Results

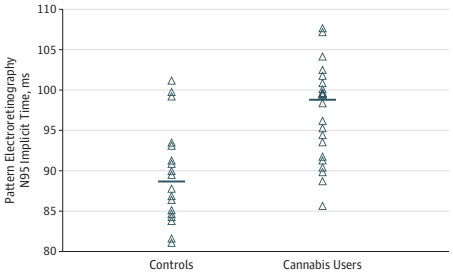
Demographic and Substance Use Characteristics

The demographic and substance use characteristics of the participants are described in the Table. There was no significant difference between controls and cannabis users for median age (cannabis users, 22 years [95% CI, 21-24]; controls, 24 years [95% CI, 23-27]; P = .13) or sex (cannabis users, 24 men [86%] and 4 women [14%]; controls, 20 men [83%] and 4 women [17%]; P = .81), but differences were noted between the groups in terms of average years of education (cannabis users, 13.5 years [95% CI, 13-14]; controls, 15 years [95% CI, 14-16]; P = .02), average number of alcohol uses per week (cannabis users, 4 [95% CI, 3-6]; controls, 1 [95% CI, 0-2]; P = .002), and median AUDIT score (cannabis users, 6 [95% CI, 4-10]; controls, 3 [95% CI, 1-4]; P < .001). Because tobacco is widely mixed with cannabis in joints, 21 of 28 cannabis users were also tobacco smokers, whereas all members of the control group were nonsmokers. More important, cannabis users were not dependent on tobacco, apart from 1 individual who was only mildly dependent.

PERG Parameters

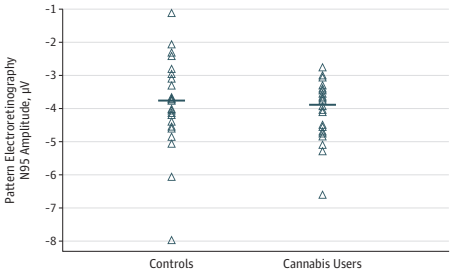
We found an increase in N95 implicit time on the results of PERG in the 28 regular cannabis users (median, 98.6 milliseconds [95% CI, 93.4-99.5]) compared with the 24 healthy controls (median, 88.4 milliseconds [95% CI, 85.0-91.1]), with 8.4

Figure 1. Dot Plot of Pattern Electroretinography N95 Implicit Time for Cannabis Users and Controls



For controls: n = 24; median implicit time, 88.4 milliseconds (95% CI, 85.0-91.1). For cannabis users: n = 28; median implicit time: 98.6 milliseconds (95% CI, 93.4-99.5). Median of the differences between the 2 groups: 8.4 milliseconds (95% CI, 4.9-11.5; $P < .001$, Mann-Whitney test). The black horizontal lines indicate medians.

Figure 2. Dot Plot of Pattern Electroretinography N95 Amplitude for Cannabis Users and Controls

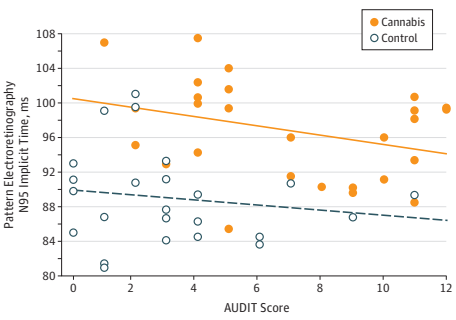


For controls: n = 24; median amplitude, −3.78 μV (95% CI, −4.45 to −3.15). For cannabis users: n = 28; median amplitude, −3.90 μV (95% CI, −4.55 to −3.60; $P = .37$, Mann-Whitney test). The black horizontal lines indicate medians.

milliseconds as the median of the differences (95% CI, 4.9-11.5; $P < .001$, Wald logistic regression) (**Figure 1**). The median N95 amplitude was -3.90 μV (95% CI, −4.55 to -3.60) in cannabis users vs -3.78 μV (95% CI, −4.45 to -3.15) in controls ($P = .37$, Mann-Whitney test) (**Figure 2**).

The logistic regression was conducted with N95 implicit time, years of education, and the AUDIT score, with cannabis users and controls as the binary outcome variable. As average number of alcohol uses per week was correlated with the AUDIT score (Spearman rank correlation, 0.736; $P < .001$), we kept the AUDIT score ($P < .001$ for the difference between controls and cannabis users vs $P = .002$ for the average number of alcohol uses per week) in this analysis. The results of the logistic regression ($\chi^2 = 40.3$; $P < .001$; Hosmer Lemeshow $\chi^2 = 6.21$; $P = .62$; 86.5% of participants correctly classified in their respective group: 89% of cannabis users and 83% of controls) showed that N95 implicit time was significant (Wald $P = .001$),

Figure 3. Interaction Between the Pattern Electroretinography N95 Implicit Time and Alcohol Use Disorders Identification Test (AUDIT) Score



Linear regression lines of N95 implicit time on the AUDIT score for controls and cannabis users. The 95% CIs of the 2 negative slopes overlap, and the lines do not cross among the ranges of the observed values (controls, −0.299 [95% CI, -1.114 to 0.516]; cannabis users, −0.517 [95% CI, -1.111 to 0.078]).

as was the AUDIT score (Wald $P = .008$), but years of education was not significant (Wald $P = .10$).

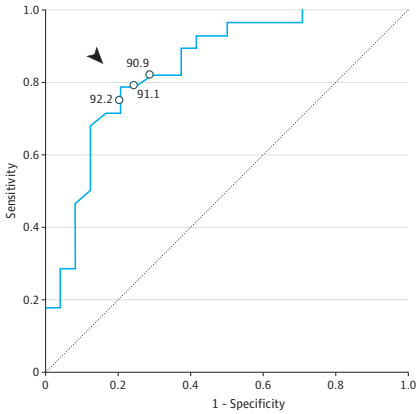
The N95 implicit time and AUDIT score were both significant between cannabis users and controls. The product AUDIT score × N95 implicit time (interaction) was not added to the model because it was too strongly correlated with the AUDIT score (Spearman rank correlation, 0.994; $P < .001$). We thus graphically investigated the interaction with 2 regression lines of N95 implicit time on the AUDIT score for controls and cannabis users (**Figure 3**). The 95% CI of the 2 slopes, which were both negative, overlapped, and the lines did not cross among the ranges of the observed values (controls, 0.299; [95% CI, -1.111 to 0.516]; cannabis users, -0.517; [95% CI, -1.114 to 0.078]).

Spearman rank correlations among all 52 participants between N95 implicit time and years of education, AUDIT score, and average number of alcohol uses per week were, respectively, −0.149 ($P = .29$), 0.093 ($P = .51$), and 0.125 ($P = .38$). Spearman rank correlations for the 28 cannabis users between N95 implicit time and number of cigarettes per day and number of packets of tobacco per year were, respectively, -0.191 ($P = .33$) and -0.165 ($P = .40$).

Sensitivity and Specificity

A receiver operating characteristic curve was used to assess the best N95 implicit time cutoff value capable of discriminating between cannabis users and controls (area under the curve, 0.84; 95% CI, 0.73-0.95; $P < .001$). Results indicated that the cutoff value giving the best balance between sensitivity and specificity for regular cannabis users and controls was 91.13 milliseconds. Twenty-two of 28 regular cannabis users were above the cutoff, with an estimated sensitivity of 78.6% (95% CI, 60.5%-89.8%), whereas 18 of 24 controls were below the cutoff, with an estimated specificity of 75.0% (95% CI, 55.1%-88.0%). Corresponding estimated positive

Figure 4. Receiver Operating Characteristic Curve Associated With N95 Implicit Time



Area under the curve = 0.84 (95% CI, 0.73-0.95; $P < .001$). For the cutoff value of 91.13 milliseconds (black arrow), 22 of 28 cannabis users are above the cutoff, with an estimated sensitivity of 78.6%, whereas 18 of 24 controls are below the cutoff, with an estimated specificity of 75.0%. For the cutoff value of 90.90 milliseconds, sensitivity = 82.1% and specificity = 70.8%; for the cutoff value of 92.23 milliseconds, sensitivity = 75.0% and specificity = 79.2%.

predictive value was 78.6% (95% CI, 60.5%-89.8%) and estimated negative predictive value was 75.0% (95% CI, 55.1%-88.0%) (**Figure 4**).

Discussion

Our results indicate that regular cannabis users appear to display an increase in N95 implicit time on PERG results with no modification in N95 amplitude. Typical PERG traces are presented in the eFigure in the Supplement. This finding provides evidence for a delay of approximately 10 milliseconds in the transmission of action potentials evoked by the RGCs. As this signal is transmitted along the visual pathway via the optic nerve and lateral geniculate nucleus to the visual cortex, this anomaly might account for altered vision in regular cannabis users.

Although this anomaly found in regular cannabis users was not associated with visual symptoms, we think it may underlie several deficits in information processing. The effects of regular cannabis use on the main cognitive functions, such as memory, attention, executive function, psychomotor function, and decision making, have been the subject of many studies.[24] For example, regular cannabis use reduces the speed of information processing, leading to attentional disorders, and can cause psychomotor retardation. Retinal processing also seems to be slowed in regular cannabis users, although, paradoxically, regular users tend to respond very quickly and impulsively during several tasks to assess risk-taking and impulsivity. This alteration detected in retinal function could be an early marker of cognitive deterioration affecting high-level cognitive functions in regular cannabis users.

Limitations

This study has several limitations. First, it is a pilot study involving a small number of participants. Consequently, PERG measurements would need to be replicated in a larger population. Second, because cannabis is widely used in conjunction with tobacco, particularly mixed together in joints, it is difficult to distinguish the effect of each compound. To our knowledge, the effect of chronic administration of nicotine on PERG results has not yet been investigated. A control group of tobacco smokers could be useful for differentiating between cannabis- and tobacco-associated effects. Third, although we found a delay in the response of the RGCs, we do not know if this delay is also detected at previous retinal stages. Full-field electroretinography measurements might be useful for addressing this issue. Similarly, another PERG component, namely P50, is of particular interest for studying macular function. We would need to assess parameters extracted from this wave—amplitude and implicit time—and its morphologic features to find out more about the effect of cannabis use on retinal functioning. Finally, in future studies involving PERG measurements, it would be important to have visual acuity of at least 20/20 in each eye. All these limitations could be addressed in the future.

Here, we assume that cannabis affected the RGC response because our results are still significant when alcohol use is integrated in statistical analysis. Although alcohol and cannabis have an opposite action on glutamatergic signaling pathways,[20,25] it cannot be ruled out that an interaction between them had an effect on the RGC response. This possibility should be explored in further studies including, for example, a control group of alcohol users. Cannabis users in our study share the same pattern as in other studies; namely, they are also alcohol users and have a lower educational level.[26,27] Finally, it would be premature to interpret the sensitivity and specificity of the findings given that our study is a pilot study involving a small number of participants.

Such alterations are found in other pathologic conditions, such as various optic neuropathic disorders, and can reveal axonal injuries or apoptosis of RGCs, which are commonly detected with tests such as PERG.[28] The fact that an increase in N95 implicit time was found with no modification in N95 amplitude suggests that the total number of cells involved in the RGC response was unchanged but argues in favor of a loss of their functional properties.[29] Accordingly, in some cases, such as optic demyelinating neuropathic conditions, modifications in the N95 wave, coupled or not with alterations in the P50 wave—the first positive PERG wave representing the macular function[22]—can discriminate between the acute or chronic state of the disease and may be of prognostic value.[29] Consequently, the P50 wave should be the subject of future study.

We suggest that these anomalies may be linked to dysfunctions in retinal glutamatergic transmission given that the effects of cannabis on glutamatergic transmission have

already been demonstrated in the central nervous system.[5,20] In addition, in the vertebrate retina, glutamate is one of the main neurotransmitters involved in the vertical transmission of retinal information[18,19] and is released by the RGCs.[30] We hypothesize that, as a result of exocannabinoids, such as tetrahydrocannabinol acting on retinal endocannabinoids, regular cannabis use may modulate the retinal level of glutamate, thus altering the retinal signal elicited by the RGCs. However, other neurotransmitter-signaling pathways expressed in the retina, such as dopaminergic and gamma-aminobutyric acid–ergic, could be targeted by exocannabinoids. Thus, other retinal electrophysiologic measurements, such as full-field electroretinography and multifocal electroretinography, could yield critical information about the effect of regular cannabis use on retinal functioning. The precise mechanisms underlying these anomalies on PERG results need to be investigated with a view to understanding the biological underpinning of retinal functional anomalies found in cannabis users.

Conclusions

To our knowledge, this is the first study to show RGC dysfunctions in regular cannabis users. Such results are particularly relevant for exploring the cerebral effect of cannabis on synaptic transmission since retinal processing is easily measurable and not affected by high-level cognitive functions. Assessments of retinal function could therefore provide valid, reliable, and reproducible measurements that could reflect cannabis-associated brain dysfunctions. Cannabis use is widespread worldwide and, consequently, the subject of great interest in terms of public health prospects. Independent of debates about its legalization, it is necessary to gain more knowledge about the different effects of cannabis so that the public can be informed. Future studies may shed light on the potential consequences of these retinal dysfunctions for visual cortical processing and whether these dysfunctions are permanent or disappear after cannabis withdrawal.

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Author Affiliations: Pôle Hospitalo-Universitaire de Psychiatrie du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France (Schwitzer, Schwan, Laprevote); EA7298 Interactions gènes-risques environnementaux et effets sur la santé, Université de Lorraine, Vandœuvre-lès-Nancy, Nancy, France (Schwitzer, Schwan, Laprevote); Institut National de la Santé et de la Recherche Médicale U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France (Schwitzer, Giersch, Lalanne); Maison des Addictions, Centre Hospitalier Régional Universitaire Nancy, Nancy, France (Schwan, Laprevote); Université de Lorraine, Faculté de Médecine, SPI-EAO, Vandoeuvre-lès-Nancy, Nancy, France (Albuisson); Centre National de la Recherche Scientifique, Institut Elie Cartan de Lorraine, Unité Mixte de Recherche 7502, Vandoeuvre-lès-Nancy, Nancy, France (Albuisson); Service d'Ophtalmologie, Centre Hospitalier Régional Universitaire Nancy, Nancy, France (Angioi-Duprez).

Author Contributions: Drs Schwitzer and Laprevote had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Schwitzer and Schwan contributed equally to this work.
Study concept and design: Schwitzer, Schwan, Albuisson, Giersch, Angioi-Duprez, Laprevote.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Schwitzer, Albuisson, Angioi-Duprez, Laprevote.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Schwitzer, Albuisson, Lalanne, Angioi-Duprez, Laprevote.
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Study supervision: Giersch, Lalanne, Angioi-Duprez, Laprevote.

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Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: The retina as a relevant site to investigate brain synaptic transmission dysfunctions

Thomas Schwitzer[a,b,c,*,1], Raymund Schwan[a,c,d,1], Karine Angioi-Duprez[e], Anne Giersch[c], Laurence Lalanne[c,i], Eliane Albuisson[f,g,h], Vincent Laprevote[a,b,c,d]

[a] Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France
[b] EA7298, INGRES, Université de Lorraine, Vandœuvre-lès-Nancy, France
[c] INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Pôle de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France
[d] Maison des Addictions, CHRU Nancy, Nancy, France
[e] Service d'Ophtalmologie, CHRU Nancy, Nancy, France
[f] Pôle S²R, PARC, BIOBASE, CHRU Nancy, Vandoeuvre lès Nancy, France
[g] Université de Lorraine, Faculté de Médecine, InSciDens, Vandoeuvre lès Nancy, France
[h] Université de Lorraine, CNRS, IECL, Nancy, France
[i] Pôle de Psychiatrie et d'addictologie, Fédération de Médecine Translationnelle de Strasbourg, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France

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ABSTRACT

Cannabis use is widespread worldwide, but the impact of smoking cannabis regularly on brain synaptic transmission has only been partially elucidated. The retina is considered as an easy means of determining dysfunction in brain synaptic transmission. The endocannabinoid system is involved in regulating retinal synaptic transmission, which might also be affected by tobacco. Previous preliminary results have shown impairments in retinal ganglion cell response in cannabis users. Here, we test the extent to which earlier retinal levels—bipolar cells and photoreceptors—are affected in cannabis users, i.e. by the association of tobacco and cannabis.

We recorded pattern (PERG) and flash (fERG) ERG in 53 regular cannabis users and 29 healthy controls. Amplitude and peak time of P50 and N95 (PERG) and of a- and b-waves (fERG) were evaluated. Cannabis users showed a significant increase in PERG N95 peak time and in fERG light-adapted 3.0 b-wave peak time, compared with controls ($p = 0.0001$ and $p = 0.002$, respectively; Mann-Whitney *U* test). No significant difference was found between the groups in terms of wave amplitude ($p = 0.525$ and $p = 0.767$ for the N95 and light-adapted 3.0 b-wave amplitude respectively; Mann-Whitney *U* test). The results demonstrated delayed ganglion and bipolar cell responses in cannabis users. These results reflect a delay in the transmission of visual information from the retina to the brain. This retinal dysfunction may be explained by an effect of cannabis use on retinal synaptic transmission. Main limitations of these results concern tobacco and alcohol use that differed between groups. The consequences of these anomalies on visual perception along with the molecular mechanisms underlying this retinal dysfunction should be explored in future human and animal studies.

1. Introduction

Regular cannabis use is a critical public health challenge, since cannabis is an addictive drug and one of the most frequently used in industrialized countries (Degenhardt et al., 2008). Cannabis is known to act on several brain synaptic transmission signaling pathways as well as tobacco (Bossong and Niesink, 2010). However, it is difficult to directly access the functioning brain and determine the long-term modulation of brain synaptic transmission following regular cannabis use. Indirect investigations are therefore needed. The retina is a particularly relevant means of access for studying the impact of regular cannabis use on brain synaptic transmission, because it is an anatomical and developmental extension of the central nervous system (CNS), previously suggested as being a good site for indirectly investigating the functioning brain in psychiatric and addictive disorders (Lavoie et al., 2014b, 2014a; Schwitzer et al., 2015a, 2016b; 2017b). Like the brain, the

* Corresponding author. Psychotherapic Center of Nancy, 1, rue du Docteur Archambault, Laxou, F-54 521, France.
E-mail address: thomas.schwitzer@univ-lorraine.fr (T. Schwitzer).
[1] Contributed equally to this work.

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retina is organized in layers of specialized neurons interconnected by synapses (Hoon et al., 2014). These retinal neurons share several anatomical and functional properties with brain neurons (Hoon et al., 2014). For example, dopaminergic, serotoninergic, glutamatergic, cholinergic and GABAergic neurotransmitters are key molecules for retinal synaptic transmission. Moreover, the human retina has a functional endocannabinoid system, which is detected in rod and cone photoreceptors and bipolar and ganglion cells (Schwitzer et al., 2015b, 2016a; Yazulla, 2008). Animal studies have shown the endocannabinoid system to be involved in regulating the release of neurotransmitters such as dopamine, serotonin, noradrenaline, glutamate and γ-aminobutyric acid (GABA) in photoreceptors and bipolar and ganglion cells (Schwitzer et al., 2015b, 2016a; Yazulla, 2008). Additionally, an experimental study in CB2 knockout mice showed changes in the fERG a- and b-wave in both scotopic and photopic conditions (Cecyre et al., 2013), suggesting that cannabinoid receptor activation due to cannabis would lead to changes in photoreceptor and bipolar cell function. Such effects may be aggravated by the intake of tobacco together with cannabis, related to its cholinergic effects, but also indirect vascular effects.

Retinal neuron function can be assessed objectively using an electroretinogram (ERG) (Holder et al., 2010). ERGs record the light-evoked electric potential originating from the retina in response to different types of stimulus (Holder et al., 2010). The recorded retinal response reflects retinal neuron signaling and is associated with changes in levels of neurotransmitters through the retina (Hoon et al., 2014). Using flash light stimuli, the flash ERG (fERG) evaluates the rod, bipolar cell and cone functions (McCulloch et al., 2015). Using alternative black and white checkerboards, the pattern ERG (PERG) evaluates ganglion cell function (Bach et al., 2013; Porciatti, 2015). Standardized protocols are available for clinical settings and research to ensure reproducible results (Bach et al., 2013; McCulloch et al., 2015). Typical fERG and PERG traces are presented in Fig. 1. Using PERG in a preliminary study, our group has recently shown a delay in the transmission of action potentials by the retinal ganglion cells in regular cannabis users compared with controls. More specifically, there was an increase in N95 peak time (Schwitzer et al., 2017a). This effect was suggested to be independent of alcohol consumption. It is now crucial to 1) confirm our findings obtained in the preliminary analysis on the total number of patients originally planned in the Causamap study, 2) investigate whether earlier retinal stages are also altered in regular cannabis users to precise where the delay of information processing is located into the retina, 3) evaluate the specificity and sensitivity of the potential functional retinal abnormalities.

The aim of this study was to verify whether early retinal stages, involving in particular bipolar and photoreceptor cells, are altered in cannabis users. Given the role of the cannabinoid system in regulating neurotransmitter release in retinal photoreceptors and bipolar and ganglion cells, we hypothesized that dysfunctions may be observed in regular cannabis users at both early and late stages of retinal processing.

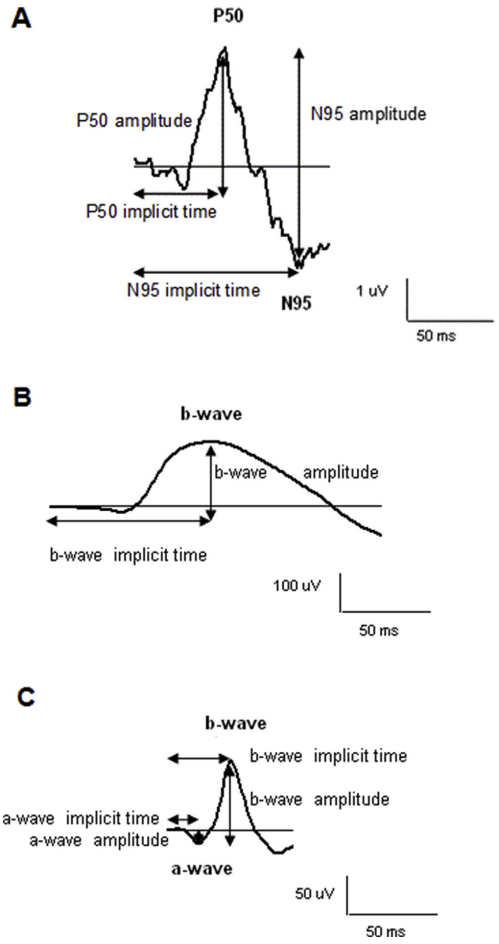

Fig. 1. Typical electroretinogram (ERG) traces obtained when assessing ganglion cell response with pattern ERG (PERG) (A), the response of the rod system with flash ERG (fERG) (B) and the response of the cone system with fERG (C). The arrows show how the parameters are measured, namely the P50, N95, a- and b-wave amplitude and peak time.

2. Material and methods

2.1. Population and ethics statement

Regular cannabis users (n = 53) and matched healthy drug-naive controls (n = 29) were recruited among the general population via a special press campaign and data were collected from February 11, 2014, to June 30, 2016. Prior to taking part in the study, volunteers provided their detailed psychoactive drug and medical history, underwent a full psychiatric evaluation, and signed consent forms detailing all aspects of the research. All participants received payment in the form of €100 in gift vouchers. The study protocol met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Nancy University Hospital. This study is part of a bigger project, Causa Map, which is researching the impact of regular cannabis use on the visual system. All participants also underwent neuropsychological assessments and EEG was recorded while performing several visual tasks.

2.2. Inclusion criteria, clinical and biological assessments

The inclusion criteria for the cannabis group were regular cannabis use equivalent to an average of at least 7 cannabis consumptions per week over the past month. The total years of cannabis use varied between 5 and 14 years with a median at 7. Others inclusion criteria included a positive urine toxicology screen for tetrahydrocannabinol (THC) metabolites, no other illicit substance use in the past month, a negative urine toxicology screen for other illicit substances, and no DSM-IV diagnosis of Axis I disorders. Since tobacco is regularly mixed

with cannabis in joints, cannabis users may meet the criteria for tobacco dependence according to the Fagerström test. Cannabis users were required to have abstained from cannabis use for at least 12 h to avoid acute cognitive dysfunction caused by cannabis use. The inclusion criteria for the healthy control subjects were no history of illicit substance use, a negative urine toxicology screen for THC metabolites and the other illicit drugs tested, and no history of DSM-IV diagnosis of Axis I psychiatric disorders. All participants were aged 18–35 years, had no history of neurological disease, no family history of schizophrenia or bipolar disorders, and were medication-free except for oral contraceptives in the case of women. They had no history of ophthalmological disease except for corrected refractive errors. All fared normally in an ophthalmic evaluation, which included visual acuity and a fundoscopic examination. Importantly, visual acuity measured with the Monoyer scale was at least 10/10 in each eye for all participants. None of the participants reported visual symptoms, and none was found to have any media opacities. If participants reported alcohol dependence based on their score in the Alcohol Use Disorders Identification Test (AUDIT) they were excluded from the study. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was used to assess current and past history of psychiatric diseases and substance use. In addition, the Cannabis Abuse Screening Test (CAST), Fagerström test and AUDIT were performed to assess use, abuse and dependence with respect to cannabis, tobacco and alcohol respectively. The extent of cannabis use was clinically assessed in an interview and a questionnaire as follows: age when regular cannabis use began, total years of cannabis use, average number of joints smoked daily and weekly over the past month and average number of grams smoked weekly (Table 1). In order to obtain objective confirmation of cannabis consumption, urine drug screens (nal von minden, Moers, Germany) were performed for cannabis, buprenorphine, benzodiazepines, cocaine, opiates, amphetamines and methadone immediately before electroretinogram testing.

2.3. Experimental protocol

PERG and fERG were performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards for PERG and fERG (Bach et al., 2013; McCulloch et al., 2015). The MonPackONE system (Metrovision, Pérenchies, France) was used for stimulation, recording and analysis. Electrical signals were recorded simultaneously from both eyes. Averaged retinal responses were first obtained from each eye and then values of parameters -peak time and amplitude-were averaged over both eyes for analysis. Electrical signals were recorded on non-dilated (PERG) and dilated pupils (fERG, Tropicamide 0.5%), with DTL electrodes (Metrovision, Pérenchies, France) placed at the bottom of the conjunctival sac. The pupil's size was noted before and after fERG recordings and remained systematically constant during the whole testing period. Ground and reference electrodes were attached to the forehead and external canthi.

Table 1
Demographic and substance use characteristics of the participants.

	Cannabis users (n = 53)	Controls (n = 29)	*P*-value
Gender (male/female) [a,d]	41/12	21/8	$p = 0.618$
Age (years) [b,c]	23 (21–30)	24 (23–27)	$p = 0.517$
Education (years) [b,c]	13 (12–14)	15 (14–16)	$p = 0.0001$
Average number of alcohol uses/week [b,c]	4 (1,5–9)	1 (0–3,5)	$p = 0.0003$
Alcohol Use Disorders Identification Test (AUDIT) scores [b,c]	7 (3,5–9)	3 (1–4,5)	$p = 0.0001$
Fagerström Test scores [b] (n = 44)	1 (0–3)	–	–
Average number of cigarettes/day [b]	4 (2–10)	–	–
Age of first cannabis use [b]	16 (15–17)	–	–
Total years of cannabis use [b]	7 (5–14)	–	–
Average number of joints/week [b]	20 (14–30)	–	–
Cannabis Abuse Screening Test (CAST) scores [b]	4 (3–5)	–	–
Average number of grams of cannabis/week [b]	4,2 (3–10)	–	–

[a] Categorical variable represented as frequencies.
[b] Quantitative variable represented as median and interquartile range.
[c] Mann-Whitney *U* test.
[d] Chi-Square test.

2.3.1. Pattern electroretinogram (PERG) measurements

A black and white contrast reversible checkerboard, with 0.8° check size, 93.3% contrast level, 100 cd/m^2 constant luminance white area, and 4 reversals per second was used. The participants were positioned 1 m from the screen. In the case of participants with refractive disorders, an appropriate optic correction was provided. At least 220 responses were recorded for each participant, with constant ambient room-lighting to achieve the best signal-to-noise ratio.

2.3.2. Flash electroretinogram (fERG) measurements

fERG recordings were performed in dark and light conditions. Participants were positioned 30 cm from the screen. They were dark-adapted for a period of 20 min before dark-adapted fERG were recorded. They were then light-adapted for 10 min to a light background set at 30 cd/m^2 (cd/m^2) managed by the MonPackONE system before light-adapted fERG was performed. At least 8 and 16 responses, for dark- and light-adapted ERG respectively, were recorded for each participant. Each retinal response is called according to the strength of the flash in candela.m^2.s^{-1}. To assess the functioning of the rod and cone system separately, dark-adapted 0.01 ERG and light-adapted 3.0 ERG were performed respectively.

2.3.3. Analysis

PERG and fERG data were analyzed with an ophthalmic monitor (Metrovision, Pérenchies, France). Analysis was performed with the experimenter blind to the status of the subject being recorded (cannabis user or control). Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. N95 is believed to reflect the response of retinal ganglion cells. P50 reflects the response of the retinal ganglion cells and macular photoreceptors and is used to evaluate the macular function. Two main parameters are derived from P50 and N95, known by convention as the amplitude measured in microvolts (μV) and the peak time (i.e. latency) measured in milliseconds (ms). N95 amplitude is measured from the trough of the N95 to the peak of the P50. P50 amplitude is measured from the trough of the inconstant N35—or from the baseline—to the peak of the P50. Peak time denotes the time taken to reach the maximum N95 and P50 amplitudes. Conversely, the two main components usually described on a typical fERG are an electronegative component, a-wave, followed by an electropositive component, b-wave. The a-wave is not detected in the dark-adapted 0.01 ERG response because it is masked by the b-wave. An a-wave is attributed to the retinal photoreceptors and a b-wave is attributed to the retinal bipolar cells, postsynaptic to photoreceptors. Two main parameters are derived from a- and b-waves, known by convention as the amplitude measured in microvolts (μV) and the peak time measured in milliseconds (ms). a-wave amplitude is measured from the baseline to the trough of the a-wave. b-wave amplitude is measured from the trough of the a-wave to the peak of the b-wave. Peak time denotes the time taken to reach the maximum a- and b-wave amplitudes. Typical traces of PERG and fERG are presented in Fig. 1.

2.4. Statistical analysis

Depending on the non-parametric distribution of several variables

included in the analyses, a Mann-Whitney *U* test, Chi-square test and Spearman's rank correlation test were used when appropriate to compare the two cannabis user/control groups or to test the association between variables. A logistic regression was performed to examine the association between the binary dependent cannabis user/control variable and the independent variables that were significant between cannabis users/controls in univariate analysis and uncorrelated. Regarding correlated variables, the most significant between cannabis users and controls was retained in the logistic regression. Regression lines were used to analyze the interaction graphically. A receiver operating characteristic (ROC) was applied to the values of the independent variables that were significant to estimate the sensitivity and specificity of cut-off values between regular cannabis users and controls. We used a conservative level of significance in comparison with alpha < 0.015%. Statistical analyses were performed using IBM-SPSS Statistics 22.0 (IBM corp.).

3. Results

3.1. Demographic and substance use characteristics

The demographic and substance use characteristics of the participants are described in Table 1. There was no relevant difference between controls and cannabis users in terms of age ($p = 0.517$) or gender ($p = 0.618$), but differences were noted between groups in terms of years of education ($p = 0.0001$; lower in cannabis users) and alcohol use (higher in cannabis users; $p = 0.0003$ for average alcohol consumption/week; $p = 0.0001$ for AUDIT score). Because tobacco is widely mixed with cannabis in joints, 44 in 53 cannabis users were also tobacco smokers, whereas all the controls were non-smokers. According to the Fagerström test, 27 in 53 cannabis users were not dependent on tobacco, 12 in 53 were slightly dependent, 4 in 53 were mildly dependent and 1 in 53 was highly dependent.

3.2. Pattern electroretinogram (PERG) parameters: N95 and P50

The median and interquartile range of the N95 peak time was 95.5 ms [91.8: 99.9] in cannabis users versus 88.9 ms [84.5: 91.1] in controls. This difference was significant between groups ($p = 0.0001$; Mann-Whitney *U* test) (Fig. 2). There was no significant difference between groups for N95 amplitude, P50 peak time and P50 amplitude (Table 2).

3.3. Full-field electroretinogram (fERG) parameters

3.3.1. Dark-adapted 0.01 ERG

There was no significant difference between groups in terms of b-wave amplitude and peak time (Table 2).

3.3.2. Light-adapted 3.0 ERG

The median and interquartile range of the b-wave peak time was 36.3 ms [35.8: 37.2] in cannabis users versus 35.8 ms [35.1: 36.3] in controls. This difference was significant between groups ($p = 0.002$; Mann-Whitney *U* test) (Fig. 3). There was no significant difference between groups for b-wave amplitude and a-wave amplitude and peak time (Table 2).

3.4. Logistic regression on 3.0 ERG b-wave peak time and N95 peak time

In order to analyze alcohol consumption and ERG parameters simultaneously and due to the significant differences in univariate analysis between cannabis user/control groups in terms of AUDIT score, average alcohol consumption/week, light-adapted 3.0 ERG b-wave peak time and N95 peak time, we conducted a logistic regression to test the association between them and cannabis users/controls as the binary outcome variable. Average alcohol consumption/week was removed due to the significant correlation (Spearman rank correlation (SCR) = 0.720: $p = 0.0001$) with the AUDIT score, which is more significant. There is no significant correlation between the AUDIT score, light-adapted 3.0 ERG b-wave peak time and N95 peak time (SCR = 0.107: $p = 0.337$ for AUDIT score *vs* N95 peak time; SCR = 0.113: $p = 0.312$ for AUDIT score *vs* light-adapted 3.0 ERG b-wave peak time and SCR = 0.177: $p = 0.111$ for N95 peak time *vs* light-adapted 3.0 ERG b-wave peak time).

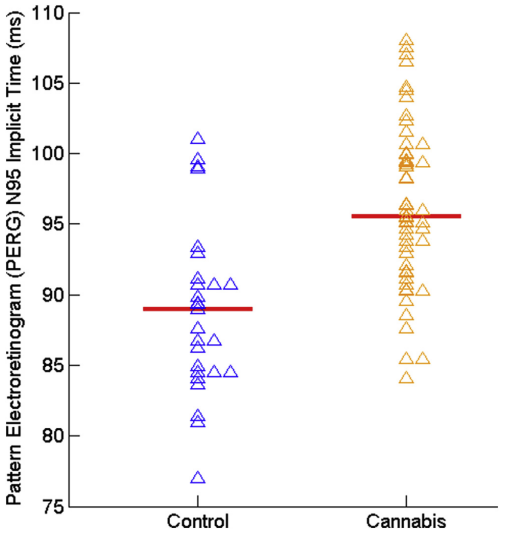

Fig. 2. Dot plot of pattern electroretinogram (PERG) N95 peak time (ms) for cannabis users (n = 53) and controls (n = 29) with medians. Cannabis users showed increased peak time and the difference between the groups is highly significant ($p = 0.0001$; Mann-Whitney *U* test).

Results of the logistic regression (N = 82; LR Chi-square = 49.81; $p = 0.0001$; Hosmer-Lemeshow Chi-square = 10.42; $p = 0.237$; 87.80% of subjects classified correctly in their respective group: 90.6% (48/53) of cannabis users and 82.8% (24/29) of controls) showed that the N95 peak time, AUDIT score and light-adapted 3.0 ERG b-wave peak time were still significant (Wald $p = 0.0001$; Wald $p = 0.001$; Wald $p = 0.010$ respectively). The AUDIT score × N95 peak time and AUDIT score × light-adapted 3.0 ERG b-wave peak time products (interactions) were not added to the model because they are too strongly correlated with the AUDIT score (SRC = 0.993: $p = 0.0001$; SRC = 0.995: $p = 0.0001$ respectively). We thus investigated these interactions graphically, for N95 peak time and for light-adapted 3.0 ERG b-wave peak time respectively, with regression lines on the AUDIT score for controls and for cannabis users. Concerning N95 peak time and the AUDIT score, the 95% confidence intervals of the two slopes, which are both negative, overlap and the lines do not cross among the ranges of the observed values (controls: −0.479; [−1.285; 0.328]; cannabis users: −0.144; [−0.625; 0.337]) (Fig. 4). Concerning light-adapted 3.0 ERG b-wave peak time, the 95% confidence intervals of the two slopes, which are both negative, overlap and the lines do not cross among the ranges of the observed values (controls: −0.023; [−0.158; 0.112]; cannabis users: −0.014; [−0.087; 0.060]) (Fig. 5).

3.5. Correlations

We conducted correlations between the ERG parameters (N95 peak time, light-adapted fERG 3.0 b-wave peak time), education level and

Table 2
Electroretinogram (ERG) parameters of the participants.

	Cannabis users (n = 53)	Controls (n = 29)	*p*-value
Pattern Electroretinogram (PERG)			
N95 peak time(ms) [a,b]	95.5 (91.8:99.9)	88.9 (84.5:91.1)	$p = 0.0001$
N95 amplitude (μV) [a,b]	−3.8 (−4.7: 3.3)	−3.7 (−4.6: 3.0)	$p = 0.525$
P50 peak time (ms) [a,b]	50.0 (48.4:53.1)	48.6 (47.1:50.8)	$p = 0.069$
P50 amplitude (μV) [a,b]	2.6 (2.2:3.0)	2.3 (2.1:2.7)	$p = 0.141$
Flash Electroretinogram (fERG)			
Dark-adapted 0.01 ERG			
b-wave peak time (ms) [a,b]	82.2 (78.7:85.2)[c]	80.9 (77.8:84.6)	$p = 0.292$
b-wave amplitude (μV) [a,b]	126.5 (112.8:146.0)[c]	133.0 (120.2:158.7)	$p = 0.188$
Light-adapted 3.0 ERG			
a-wave peak time (ms) [a,b]	18.6 (18.6:19.0)	18.6 (18.1:19.0)	$p = 0.080$
a-wave amplitude (μV) [a,b]	−10.2 (−11.7: 8.8)	−10.8 (−12.6: 9.2)	$p = 0.216$
b-wave peak time (ms) [a,b]	36.3 (35.8:37.2)	35.8 (35.1:36.3)	$p = 0.002$
b-wave amplitude (μV) [a,b]	45.4 (40.7:51.2)	48.0 (39.4:51.9)	$p = 0.767$

[a] Quantitative variable represented as median and interquartile range.
[b] Mann-Whitney *U* test.
[c] n = 52.

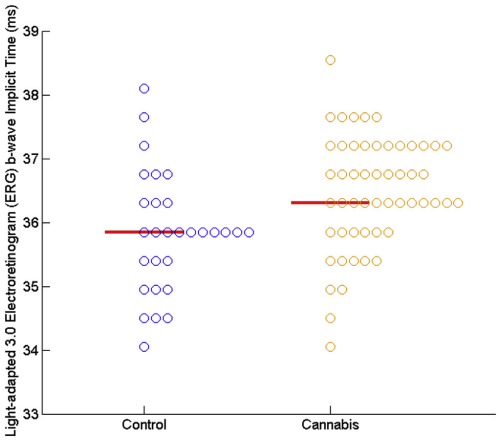

Fig. 3. Dot plot of flash electroretinogram (fERG) light-adapted 3.0 b-wave peak time (ms) for cannabis users (n = 53) and controls (n = 29) with medians. Cannabis users showed increased peak time and the difference between the groups is highly significant ($p = 0.002$; Mann-Whitney *U* test).

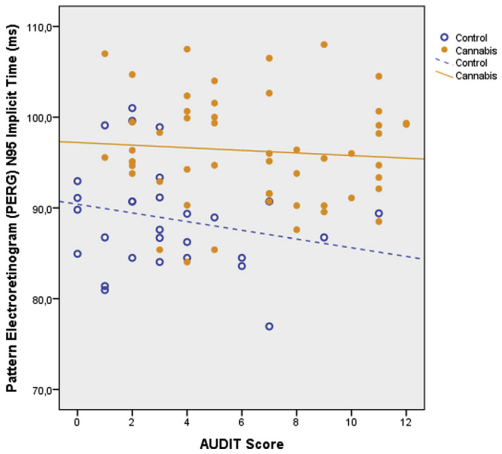

Fig. 4. Graphical investigation of the interaction between the pattern electroretinogram (PERG) N95 peak time and the AUDIT score. Linear regression lines of N95 peak time (ms) on the AUDIT score for controls (n = 29) and for cannabis users (n = 53). The 95% confidence intervals of the two negative slopes overlap and the lines do not cross among the ranges of the observed values (controls: −0.479; [−1.285; 0.328]; cannabis users: −0.144; [−0.625; 0.337]).

alcohol consumption (AUDIT score). The correlations were evaluated in the whole sample of subjects as well as in each group. None of these correlations was significant at a level of 0.015.

3.6. Sensitivity and specificity of light-adapted 3.0 ERG b-wave peak time and N95 peak time

An ROC was used to assess the best cut-off value of N95 peak time and of light-adapted 3.0 ERG b-wave peak time, capable of discriminating between cannabis users and controls. The results indicated that the cut-off value for N95 peak time giving a good balance between sensitivity and specificity for regular cannabis users and controls was 91.3 ms (Area under the curve (AUC) = 0.83; 95% CI [0.73; 0.92]; $p = 0.0001$). Six out of 29 controls are below the cut-off, with an estimated specificity of 79.3% (95% CI [0.62; 0.90]) whereas 11 out of 53 regular cannabis users are above the cut-off, with an estimated sensitivity of 79.2% (95% CI [0.67; 0.88]). The results indicate that the cut-off value for light-adapted 3.0 ERG b-wave peak time giving a good balance between sensitivity and specificity for regular cannabis users and controls was 36.1 ms (AUC = 0.71; 95% CI [0.58; 0.83]; $p = 0.002$). Twenty out of 29 controls are below the cut-off, with an estimated specificity of 69% (95% CI [0.51; 0.83]), whereas 38 out of 53 regular cannabis users are above the cut-off, with an estimated sensitivity of 71.7% (95% CI [0.58; 0.82]) (Fig. 6).

4. Discussion

We found delayed retinal processing in regular cannabis users compared with controls in two critical stages, namely bipolar and ganglion cells. These results suggest a delay of approximatively 6 ms in the emission of action potentials by the retinal ganglion cells in cannabis users, shown by an increase in PERG N95 peak time. Another finding of this study is the delay observed in regular cannabis users in the response of cone bipolar cells—an earlier stage of retinal processing—shown by an increase in the b-wave peak time of the light-

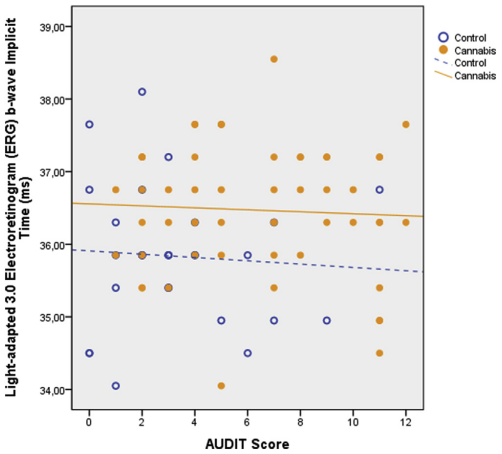

Fig. 5. Graphical investigation of the interaction between the flash electroretinogram (fERG) light-adapted 3.0 b-wave peak time and the AUDIT score. Linear regression lines of fERG light-adapted 3.0 b-wave peak time (ms) on the AUDIT score for controls (n = 29) and for cannabis users (n = 53). The 95% confidence intervals of the two negative slopes overlap and the lines do not cross among the ranges of the observed values (controls: −0.023; [-0.158; 0.112]; cannabis users: −0.014; [-0.087; 0.060]).

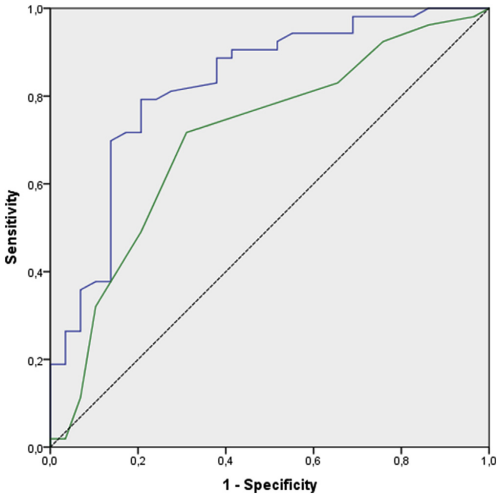

Fig. 6. Receiver operating characteristic (ROC) curves. A) The blue curve is related to N95 peak time. AUC = 0.83; 95% CI [0.73; 0.92]; $p = 0.0001$ for the cut-off value of 91.3 ms (6 out of 29 controls are below the cut-off, with an estimated specificity of 79.3% (95% CI [0.62; 0.90]) whereas 11 out of 53 regular cannabis users are above the cut-off, with an estimated sensitivity of 79.2% (95% CI [0.67; 0.88])). B) The green curve is related to light-adapted 3.0 ERG b-wave peak time. AUC = 0.71; 95% CI [0.58; 0.83]; $p = 0.002$ for the cut-off value of 36.1 ms (20 out of 29 controls are below the cut-off, with an estimated specificity of 69% (95% CI [0.51; 0.83]), whereas 38 out of 53 regular cannabis users are above the cut-off, with an estimated sensitivity of 71.7% (95% CI [0.58; 0.82]). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

adapted 3.0 fERG. This result supports a delay in the gradual variation of membrane potential in cone bipolar cells of approximatively 0.5–1 ms in cannabis users in comparison with controls. No anomaly was observed in either rod and cone photoreceptors or in bipolar cells connected to the rod receptors.

We observed an increase in N95 and b-wave peak time. According to these findings, ganglion cells and bipolar cells of the cone system take longer to react to a light stimulation when under the influence of regular cannabis use. Moreover, anomalies in peak time occur with no change in amplitude, which suggests that the total number of cells involved in the visual response is preserved, but that their functional properties are impaired. The N95 anomalies confirm our earlier findings; the signal sent to the brain by the optic nerve formed by the axons of the ganglion cells is delayed. In addition, these results suggest that this delay exists already at an earlier retinal stage, i.e. at a post-receptoral level in the bipolar cells of the cone system. It seems to be amplified in ganglion cells by ≈ 6 ms. Although regular cannabis users did not report visual symptoms or visual deficits, these findings may imply that information is processed less rapidly, psychomotor retardation and attentional disorders, described commonly in regular cannabis users (Broyd et al., 2016). The retinal abnormalities are not correlated with clinical observations, but they could serve as early functional markers of the impact of the combined use of cannabis and tobacco on brain synaptic transmission. Why P50 peak time is not altered worth to be discussed. This is probably due to the fact that the exact origin of this wave is not affirmed with certainty. P50 would be in part related to retinal ganglion cell function and to photoreceptors and bipolar cells function situated in the macula (Holder et al., 2010). Retinal impairments have already been proposed as indicators of neurological dysfunctions in CNS disorders (London et al., 2013). For example, in multiple sclerosis, Parkinson's disease and Alzheimer's disease, ganglion cell dysfunctions often precede brain dysfunctions and may constitute early markers of brain dysfunction (Celesia et al., 1986; Froehlich and Kaufman, 1993, 1994; Garcia-Martin et al., 2014; Holder et al., 2009; Krasodomska et al., 2010; Parisi et al., 2001; Peppe et al., 1995, 1998). In another hand, a significant reduction in retinal contrast gain measured with PERG measurements was found in unmedicated and medicated depressed patients independently of the antidepressant therapy, in comparison with the control group (Bubl et al., 2015, 2012, 2010).

When performing an ROC analysis on both N95 peak time and light-adapted 3.0 ERG b-wave peak time, we observed that the parameter capable of classifying both cannabis users and controls correctly in their corresponding group with the best specificity and sensitivity is the N95 peak time. In comparison with the ROC analysis performed in our preliminary study on the N95 peak time, we found that the cutoff value (91.3 ms vs 91.1 ms), sensitivity (79.2% vs 78.6%) and specificity (79.3% vs 75%) are noticeably similar and thus could give support to the reliability and reproducibility of the findings. It would be inappropriate, at this time of research, to use these data as markers to separate patients from controls in the general population. However, they can be viewed as an interesting trail to follow in order to study central neurotransmission dysfunctions in cannabis users.

Cannabis is a neuromodulator substance that acts directly and indirectly on several synaptic transmission signaling pathways, and especially on glutamatergic synaptic transmission (Bossong and Niesink, 2010). Glutamate is one of the key neurotransmitters detected in the retina and is known to be involved in the vertical transmission of the retinal signal from photoreceptors to ganglion cells (de Souza et al., 2013). Bipolar cells of the cone system and ganglion cells, which function less effectively in cannabis users, both have a functional cannabinoid system (Schwitzer et al., 2015b, 2016a; Yazulla, 2008). This system helps to regulate synaptic transmission in these cells. We suggest that tetrahydrocannabinol (THC) may alter synaptic transmission in these cells and delay the cellular response by acting directly on the cannabinoid receptors in bipolar and ganglion cells. Previous findings in humans and in animals support this hypothesis. Strong labeling of

CB1 has been detected in human photoreceptors, whereas human bipolar and ganglion cells were moderately stained for CB1 (Straiker et al., 1999). Since bipolar and ganglion cells have lower levels of CB1 than photoreceptors, they may be more sensitive to the effect of THC on synaptic transmission. In mice retinal ganglion cells, the exogenous cannabinoid WIN 55212-2 induced a significant reduction in the frequency of spontaneous postsynaptic currents in retinal ganglion cells, through a presynaptic action on glutamatergic transmission (Middleton and Protti, 2011). These data speak in favor of delayed ganglion cell processing due to a cannabinoid agonist effect, which we have confirmed here in humans.

Following our previous preliminary study (Schwitzer et al., 2017a), we also evaluated the potential effect of alcohol consumption on our results. Delayed retinal responses remained significant when alcohol consumption was integrated into the statistical analysis. This suggests an isolated and independent effect of cannabis use on retinal function. Higher alcohol consumption is common in regular cannabis users compared with controls (Meier et al., 2012). Alcohol and cannabis are two neuromodulator substances that act on CNS synaptic transmission signaling pathways. Therefore, when studying the effect of cannabis on CNS synaptic transmission, distinguishing its effect from the consequence of alcohol intake is crucial. Ideally, a control group of alcohol users would be useful to accurately evaluate the impact of alcohol consumption on retinal processing. The educational level was not integrated into the statistical analysis because it is most likely that it cannot alter the retinal functioning.

In addition to alcohol, tobacco is another substance that acts on CNS synaptic transmission and is consumed by regular cannabis users, particularly with cannabis in joints (Agrawal et al., 2012). Therefore, future studies should research this bias with a control group including tobacco smokers. The effect of chronic nicotine administration on ERG has not yet been evaluated. Dark-adapted and light-adapted fERG responses have been modified after acute nicotine administration in the form of gum 30 min before testing (Varghese et al., 2011), but the effect of regular tobacco use on fERG measurements still needs to be evaluated. Correlations performed in this study did not show an effect of tobacco on retinal function, but an indirect effect or an interaction with the effect of cannabis cannot be excluded. It remains a fact, though, that neuronal signaling is slowed down in cannabis users.

In summary, regular cannabis users showed slower retinal processing than the controls, a delay that stems from delayed bipolar and ganglion cell responses. Theses anomalies are underpinned by dysfunctions in retinal synaptic transmission caused by regular cannabis use. Molecular and genetic studies of the precise mechanisms underlying these retinal dysfunctions should be included in future research in this field. Since the retina is a crucial site for investigation of brain synaptic transmission abnormalities in psychiatric and addictive disorders, these perspectives could help us understand the effects of cannabis on brain synaptic transmission. If brain synaptic dysfunctions are detected in the retina, these data could be particularly relevant because they may contribute to the development of pharmacotherapy for cannabis use disorder (CUD), for which there is no validated pharmacotherapy for CUD treatment.

Conflicts of interest

All the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Contributors

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Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use

Alice Lucas[a,1], Audrey Thirion[a,1], Raymund Schwan[a,b,c], Julien Krieg[c], Karine Angioi-Duprez[d], Vincent Laprevote[a,b,c], Thomas Schwitzer[a,c,*]

[a] Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France
[b] Maison des Addictions, CHRU Nancy, Nancy, France
[c] INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France
[d] Service d'Ophtalmologie, CHRU Nancy, Nancy, France

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ABSTRACT

Background: Cannabis consumption is widespread across the world, and the co-occurrence of cannabis use and alcohol consumption is common. The study of background noise - resting-state neural activity, in the absence of stimulation - is an approach that could enable the neurotoxicity of these substances to be explored. Preliminary results have shown that delta-9-tetrahydrocannabinol (Δ9-THC) causes an increase in neural noise in the brain. Neurons in the brain and the retina share a neurotransmission system and have similar anatomical and functional properties. Retinal function, evaluated using an electroretinogram (ERG), may therefore reflect central neurochemistry. This study analyses retinal background noise in a population of regular co-occurrent cannabis and alcohol consumers.

Methods: We recorded the flash ERGs of 26 healthy controls and 45 regular cannabis consumers, separated into two groups based on their alcohol consumption: less than or equal to 4 glasses per week (CU ≤ 4) or strictly > 4 glasses per week (CU > 4). In order to extract the background noise, the Fourier transform of the pseudo-periodic and sinusoidal signals of the 3.0 flicker-response sequence was calculated. This sequence represents the vertical transmission of the signal from cones to bipolar cells. The magnitude of the background noise is defined as the average of the magnitudes of the two neighbouring harmonics: harmonic −1 (low frequency noise) and harmonic +1 (high frequency noise).

Results: The magnitude of harmonic −1 was significantly increased between the groups CU > 4 (6.78 (± 1.24)) and CU ≤ 4 (5.69 (± 1.80)) among regular users of cannabis and alcohol. A significant increase in the average magnitude of the two harmonics was found between the groups CU > 4 (5.12 (± 0.92)) and CU ≤ 4 (4.36 (± 1.14)). No significant difference was observed with regard to the magnitude of the harmonic +1.

Conclusions: The increase in background noise may reflect the neurotoxicity of cannabis, potentiated by alcohol consumption, on retinal neurons dynamic. This neural disruption of the response generated by retinal stimulation may be attributable to altered neurotransmitter release.

1. Introduction

Cannabis is the third most commonly used psychoactive substance in the world after alcohol and tobacco (Degenhardt et al., 2008). Co-occurrence of alcohol consumption in regular consumers of cannabis is common (Meier et al., 2012). Cannabis and alcohol are both neurotoxic substances that may potentiate each other's effects, justifying the investigation of their toxicity both alone and in combination (Broyd et al., 2016). In particular, they are responsible for altered synaptic transmission (Bossong and Niesink, 2010; Schwitzer et al., 2016a). The mechanisms of action of their neurotoxicity are the subject of many scientific papers in the field of neuroscience.

Studying background noise is an innovative approach to exploring this neurotoxicity. Background noise represents the neural electrical

* Corresponding author at: Psychotherapic Center of Nancy, 1, rue du Docteur Archambault, Laxou F-54 521, France.
E-mail address: thomas.schwitzer@univ-lorraine.fr (T. Schwitzer).
[1] Contributed equally to this work.

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activity recorded without visual stimulation (Meigen and Bach, 1999). In the brain, acute cannabis use increases neural noise, i.e. neural electrophysiological activity in the pre-stimulation period, disrupting the performance of cognitive tasks. The effects are mediated by the endocannabinoid system (Cortes-Briones et al., 2015; Laprevote et al., 2017). To our knowledge, the impact of alcohol on neural noise has not been studied.

This study aims to use the retina as a site for the indirect investigation of cerebral neurotransmission by means of retinal background noise in people who use cannabis and alcohol concomitantly. The retina is an anatomical and developmental extension of the central nervous system (Schwitzer et al., 2015a; Hoon et al., 2014; Schwitzer et al., 2017a; London et al., 2013). It has a functional endocannabinoid system that is involved in the regulation of retinal neurotransmission (Hoon et al., 2014; Schwitzer et al., 2015a, 2017a, 2016b; London et al., 2013). In particular, its neurotransmission system shares similarities with the brain transmission system. The neurotransmission system comprises the principal neurotransmitters involved in substance consumption: glutamate, gamma-aminobutyric acid (GABA) and dopamine to name but a few (Schwitzer et al., 2016b). These neurotransmitters are involved in the vertical transmission of retinal signals, thus enabling the propagation of visual information captured by photoreceptors to its transmission to the visual processing centers within the brain (Schwitzer et al., 2015b). The retina may therefore offer functional markers for the abnormalities of cerebral neurotoxicity (Schwitzer et al., 2016c).

Retinal function may be measured using an electroretinogram (ERG). The ERG records electrophysiological signals responding to various types of light stimuli (McCulloch et al., 2015). The response generated reflects the average electrical potential generated by populations of neurons and is associated with changes to the levels of their neurotransmitters (Holder et al., 2010). Regular cannabis users have delayed signal processing in the retina versus healthy volunteers, as a result of delayed ganglion and bipolar cell responses (Schwitzer et al., 2018; Schwitzer et al., 2017b). Alcohol-induced retinal toxicity might also cause delayed processing of retinal signals (McKellar et al., 1997; Ikeda, 1963). This is a consequence of changes to the organization of the bipolar cell layer (McKellar et al., 1997). These anomalies - the consequences of cannabis and alcohol use - are supported by malfunctions of the synaptic transmission in the retina caused by regular use of these substances.

This is the first study assessing retinal background noise in regular, co-occurrent users of cannabis and alcohol. The objective of our study is to compare the background noise recorded using flash ERG of regular cannabis users divided into two populations according to their level of alcohol consumption, and a population of healthy volunteers. Our hypothesis is that background noise is increased in regular users of cannabis and on the basis of their level of alcohol consumption.

2. Methods and materials

2.1. Population and ethics statement

Regular cannabis users ($n = 56$) and matched healthy drug-naive controls ($n = 29$) were recruited among the general population via a special press campaign and data were collected from February 11, 2014, to June 30, 2016. Among participants, data of 14 participants (11 cannabis users and 3 controls) were excluded because of lacking data or uninterpretable, then 45 cannabis users and 26 controls were included in this study. The 45 regular cannabis users were separated into two groups according to the median of the number of alcohol uses/week ($=4$), as follows: a group of 24 regular cannabis users with a number of alcohol uses/week strictly higher than 4 ($CU > 4$) and a group of 21 regular cannabis users with a number of alcohol uses/week equal to or < 4 ($CU \leq 4$). Prior to taking part in the study, volunteers provided their detailed psychoactive drugs and medical history, underwent a full psychiatric evaluation, and signed consent forms detailing all aspects of the research. All of the participants received payment in the form of €100 in gift vouchers. The study protocol met the requirements of the Helsinki Declaration and was approved by the Ethics Committee of Nancy University Hospital. This study is part of a bigger project, Causa Map, which is researching the impact of regular cannabis use on the visual system. All participants also underwent neuropsychological assessments and EEG recordings during several visual tasks.

2.2. Inclusion criteria, clinical and biological assessments

The inclusion criteria for the cannabis group were regular cannabis use at the rate of at least 7 cannabis consumptions per week over the past month, a positive urine toxicology screen for tetrahydrocannabinol (THC) metabolites, no other illicit substance use in the past month, a negative urine toxicology screen for other illicit substances, and no DSM-IV diagnosis of Axis I disorders. Since tobacco is regularly mixed with cannabis in joints, cannabis users may meet the criteria for tobacco dependence according to the Fagerström test. Cannabis users were required to present at least 12 h of abstinence of cannabis use so that there were no acute cognitive dysfunctions due to cannabis use. The inclusion criteria for the healthy control subjects were no history of illicit substance use, a negative urine toxicology screen for THC metabolites and other illicit drugs tested, and no history of DSM-IV diagnosis of Axis I psychiatric disorders. All participants were aged 18 to 35 years, had no history of neurological disease, no family history of schizophrenia or bipolar disorders, and were medication-free except for oral contraceptives in the case of women. They had no history of ophthalmological disease except for corrected refractive errors. All of them fared normally in an ophthalmic evaluation which included visual acuity and a fundoscopic examination. Importantly, visual acuity measured with the Monoyer Scale was at least 10/10 in each eye for all participants. None of the participants reported visual symptoms, and none was found to have any media opacities. If participants reported an alcohol dependence according to their score in the Alcohol Use Disorders Identification Test (AUDIT) they were excluded from the study. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was administered to assess current and past history of psychiatric diseases and substance use. In addition, the Cannabis Abuse Screening Test (CAST), Fagerström Test, and AUDIT were performed to assess use, abuse or dependence with respect to cannabis, tobacco and alcohol, respectively. The extent of cannabis use was clinically assessed in an interview and a questionnaire as follows: age when regular cannabis use began, total years of cannabis use, average number of joints smoked daily and weekly over the past month, average number of grams smoked weekly. In order to obtain objective confirmation of cannabis consumption, urine drug screens (Nal von Minden, Moers, Germany) were performed for cannabis, buprenorphine, benzodiazepines, cocaine, opiates, amphetamines and methadone immediately before electroretinogram testing.

2.3. Experimental protocol

2.3.1. Flash electroretinogram (fERG) measurements

fERG was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards for fERG (McCulloch et al., 2015). The MonPackOne system (Metrovision, Perenchies, France) was used for stimulation, recording and analysis. Electrical signals were recorded simultaneously from both eyes (averaged for analysis), on dilated pupils (fERG, Tropicamide 0, 5%), with DTL electrodes (Metrovision, Perenchies, France) placed at the bottom of the conjunctival sac. The pupil's size was noted before and after fERG recordings and remained systematically constant during the whole testing period. Ground and reference electrodes were attached to the forehead and external canthi.

The standard fERG protocol comprises 5 sequences. This analysis

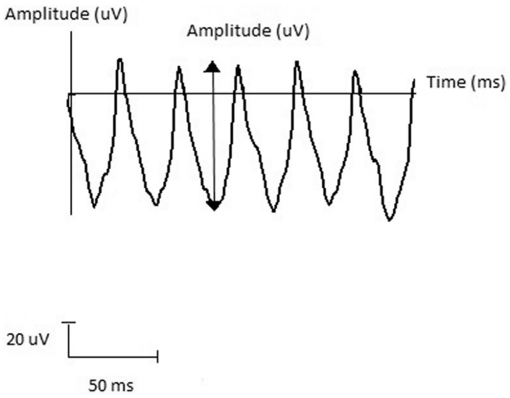

Fig. 1. Typical fERG traces obtained when assessing the 3.0 flicker response. The arrow represents the wave amplitude.

will look at the flicker 3.0 response sequence, which specifically provides information on the status of the transmission of the cone response to their ON and OFF bipolar cells. In line with the ISCEV guidelines, the Flicker 3.0 ERG sequence was performed in light conditions and the standard flash was delivered at a temporal frequency of 30 Hz. This stimulation frequency means that the response of a specific neuron subpopulation - L and M cones - can be isolated and their physiological properties exploited (Fig. 1).

Participants were positioned 30 cm from the screen. They were then light-adapted for 10 min to a light background set at 30 cd/m^2 (cd/m^2) provided by MonPackOne system before light-adapted fERG was performed. At least 16 responses were recorded for each participant and were extracted from the same sequence named the Flicker sequence of the flash ERG, as recommended by international guidelines.

2.3.2. Analysis

The recording duration for each test was 225 ms, divided into 25 ms in the pre-stimulation period and up to 200 ms in the post-stimulation period. The sampling frequency was 1138 Hz. The tracing obtained was taken from the averaging of the electrophysiological activity across the tests. The final signal had a pseudo-periodic and sinusoidal appearance. Frequency analysis of the averaged signal was carried out using the software program MATLAB (MathWorks). On the basis of the literature concerning the distribution and spectral properties of background noise, we have calculated the Fourier transform of the averaged signal for each subject using the proposed mathematical methods (Meigen and Bach, 1999). This gives a Time-Frequency spectrum with a frequency resolution of 4.46 Hz. The Fourier transform breaks down a periodic function into a sum of sinusoidal functions called harmonics, which have different magnitudes, measured in microvolts (μV). This enables the part of the signal at the dominant frequency of the stimulation - called fundamental frequency - to be distinguished from the background noise. It is therefore possible to carry out frequency analysis and selectively extract the dominant frequency of the stimulation and its harmonics. We thus extracted the magnitude of the spectrum at the frequency of the stimulus to evaluate the ratio of signal to noise on the recordings. The magnitude of noise was defined as the average of the magnitudes of the two neighbouring harmonics at 30 Hz +/− 4.46 Hz, i.e. a harmonic ~10% higher and one ~10% lower than the stimulus frequency. The harmonic 10% lower was called harmonic −1 and the harmonic 10% higher was called harmonic +1. The signal-to-noise ratio (SNR) -which could also be named the signal-to-harmonics ratio- was thus calculated by dividing the amplitude of the fundamental by the average of the amplitudes of the adjacent harmonics (Meigen and Bach, 1999) (Fig. 2).

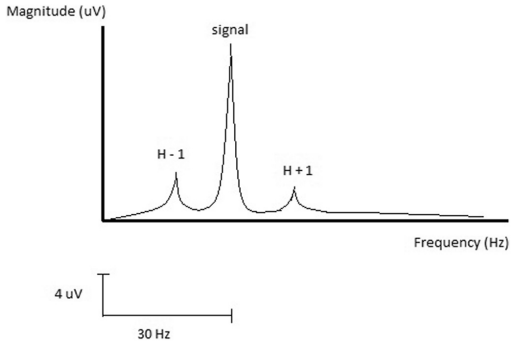

Fig. 2. Trace obtained after Fourier analysis. The noise magnitude is defined as the average noise magnitude at the two neighbouring frequencies (H-1 and H + 1).

2.4. Statistical analysis

Depending on the parametric distribution of variables included in the analyses, a Student test, Chi-square test, Analysis of variance (ANOVA) test and Post hoc comparison with Tukey test were used when appropriate to compare the three groups or to test the association between variables. We used a conservative level of significance in comparison with alpha < 0.05%. Statistical analyses were performed using STATISTICA 8.0 (StatSoft, Inc.).

3. Results

3.1. Demographic and substance use characteristics

The demographic and substance use characteristics of the participants are described in Table 1. There was no significant difference between the 3 groups in terms of age (p = 0,95), gender (p = .19 for CU > 4 vs CU < 4; p = .38 for CU > 4 vs controls and p = .63 for CU < 4 vs controls, chi square test), but differences were noted between groups in terms of years of education (F(2,68) = 41,38; p < 0,05) and alcohol use (F(2,68) = 7,42; p < 0,05 for average alcohol consumption/week and F(2,68) = 28,01; p < 0,05 for AUDIT score). Post hoc analyses with Tukey test, when appropriate, were presented in Table 1.

Because tobacco is widely mixed with cannabis in joints, 39 in 45 cannabis users were also tobacco smokers, whereas all the controls were non-smokers. According to the Fagerström test, 32 in 45 cannabis users were not dependent on tobacco, 9 in 45 were slightly dependent, 4 in 45 were mildly dependent and 0 in 45 was highly dependent.

3.2. ERG parameters

The mean and standard deviation of the magnitude of the harmonic −1 was 6,07 (+/− 1,27) in controls versus 6,78 (± 1,24) in CU > 4 versus 5,69 (± 1,80) in CU ≤ 4. The magnitude of the harmonic −1 was significantly different between the 3 groups (F(2.68) = 3,87, p < 0,05, ANOVA test). Post hoc comparison with Tukey test showed that magnitude of the harmonic −1 significantly differed between CU ≤ 4 and CU > 4 (p < 0,05), but it failed to show any difference between controls and CU > 4 (p = .19) and between controls and CU ≤ 4 (p = .64) (Fig. 3).

The mean and standard deviation of the magnitude of the harmonic

Table 1
Demographic and substance use characteristics of the participants.

	Cannabis users with > 4 alcohol uses/ week (CU > 4, *n* = 24)	Cannabis users with ≤ 4 alcohol uses/week (CU ≤ 4, *n* = 21)	Controls (n = 26)	*P*-value	P-value: Tukey test CU > 4 and CU ≤ 4	P-value: Tukey test CU > 4 and controls	P-value: Tukey test CU ≤ 4 and controls
Gender (male/female)[a,d]	20/4	14/7	19/7	*NS*	_	_	_
Age (years)[b,c]	25,6 (7,4)	25,1 (4,9)	25,2 (4,3)	*NS*	_	_	_
Education (years)[b,c]	13,6 (1,5)	13,0 (2,4)	15,0 (1,7)	$p < 0,05$	*NS*	$p < 0,05$	$p < 0,05$
Average number of alcohol uses/week[b,c]	13,6 (8,2)	2,1 (1,3)	1,9 (2,7)	$p < 0,05$	$p < 0,05$	$p < 0,05$	*NS*
Alcohol Use Disorders Identification Test (AUDIT) scores[b,c]	8,9 (2,5)	4,4 (3,0)	3,2 (2,8)	$p < 0,05$	$p < 0,05$	$p < 0,05$	*NS*
Fagerström Test scores[b,e]	1,8 (2,0)	1,4 (1,7)	_	*NS*	_	_	_
Average number of cigarettes/ day[b,e]	6,6 (5,6)	4,6 (5,0)	_	*NS*	_	_	_
Age of firts cannabis use[b,e]	16,1 (1,2)	16,0 (1,7)	_	*NS*	_	_	_
Total years of cannabis use[b,e]	9,5 (7,3)	9,1 (5,1)	_	*NS*	_	_	_
Average number of joints/ week[b,e]	23,0 (15,7)	27,7 (23,7)	_	*NS*	_	_	_
Cannabis Abuse Screening Test (CAST) scores[b,e]	4,2 (1,0)	3,7 (1,4)	_	*NS*	_	_	_
Average number of grams of cannabis/week[b,e]	7,0 (8,7)	5,0 (4,3)	_	*NS*	_	_	_

NS = non significant.
[a] Categorical variable represented as frequencies.
[b] Quantitative variable represented as mean and standard deviation.
[c] Analysis of variance (ANOVA) test.
[d] Chi-Square test.
[e] Student test.

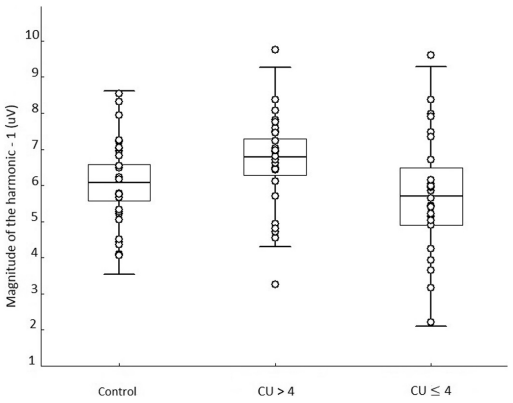

Fig. 3. Box plot of magnitude of the harmonic −1 for cannabis users with > and ≤ 4 alcohol uses / week and control with mean and standard deviation. For controls: $n = 26$; mean: 6,07 µV; DS ± 1,27. For CU > 4: $n = 24$; mean: 6,78 µV; DS ± 1,24. For CU ≤ 4: $n = 21$; mean: 5,69 µV; DS ± 1,80. Small disks represent the individual data points.

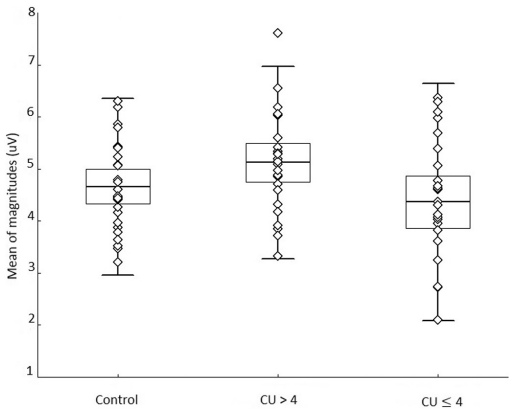

Fig. 4. Box plot of magnitude of the retinal background noise for cannabis users with > and ≤ 4 alcohol uses / week and control with mean and standard deviation. For controls: n = 26; mean: 4,66 µV; DS ± 0,85. For CU > 4: n = 24; mean: 5,12 µV; DS ± 0,92. For CU ≤ 4: n = 21; mean: 4,36 µV; DS ± 1,14. Small diamonds represent the individual data points.

+1 was 3,25 (± 0,79) in controls versus 3,46 (± 0,88) in CU > 4 versus 3,04 (± 0,79) in CU ≤ 4. The magnitude of the harmonic +1 was not significantly different between the 3 groups ($F(2.68) = 1.4996$, $p = .23$, ANOVA test).

The mean and standard deviation of the background noise was 4,66 (± 0,85) in controls versus 5,12 (± 0,92) in CU > 4 versus 4,36 (± 1,14) in CU ≤ 4. The magnitude of the background noise was significantly different between the 3 groups ($F(2.68) = 3.53$, $p < 0,05$, ANOVA test). Post hoc comparison with Tukey test showed that background noise significantly differed between CU ≤ 4 and CU > 4 ($p < 0,05$), but it failed to show any difference between controls and CU > 4 ($p = .22$), and between controls and CU ≤ 4 ($p = .55$) (Fig. 4).

4. Discussion

The results of this study highlight an increase in retinal background noise at low frequency harmonic during stimulation, i.e. which could reflect a transient slow-down dynamic of the retinal neuronal response in users with co-occurrent consumption of cannabis and alcohol. This is an indicator of a background neural activity disturbance and a disruption of the retinal neurons cue following visual stimulation. This increase in background retinal noise is apparently an effect of the potentiation of the neurotoxic properties of cannabis and alcohol in a population where the subjects present co-occurrent consumption.

We have observed that the average magnitudes of the two

harmonics is significantly increased between the CU > 4 and CU ≤ 4 groups, reflecting an increase in overall retinal background noise in regular concomitant users of alcohol and cannabis, throughout the cellular response. A significant increase in the magnitude of harmonic −1 is thus found between the CU > 4 and CU ≤ 4 groups, indicating an increase in retinal background noise during visual stimulation. But no significant difference was observed with regard to the magnitude of harmonic +1 between the three groups, which signifies that no disruption in neural activity at high frequency background noise was shown between the groups. The increase in low frequency noise indicates a possible hampering of the total neural activity. Furthermore, no significant difference was found between the control group and the CU > 4 group, nor between the control group and the CU ≤ 4 group, regardless of the variable studied. This could reflect an effect of the potentiation of the neurotoxicity of the two substances, alcohol and cannabis, on retinal neural activity rather than an effect of the neurotoxicity of cannabis alone.

The ERG is a test that could enable synaptic transmission anomalies in the retina as a result of regular cannabis use to be studied (Schwitzer et al., 2016a; Schwitzer et al., 2015a; Schwitzer et al., 2017a; Schwitzer et al., 2016c; Schwitzer et al., 2018; Schwitzer et al., 2017b; Laprevote et al., 2015a; Laprevote et al., 2015b). Furthermore, using fERG and pattern- ERG (PERG, reversing checkerboard), our group showed a significant increase in both PERG N95 and fERG b-wave implicit time with no change in amplitude in regular cannabis users versus healthy volunteers. These results reflect slowed processing of retinal information at the level of the ganglion and ON-bipolar cells (Schwitzer et al., 2018; Schwitzer et al., 2017b). These anomalies may be supported by malfunctions of the synaptic transmission in the retina caused by regular cannabis consumption. Thus, THC, through direct action on the cannabinoid receptors found in the ganglion and ON-bipolar cells, could alter synaptic transmission and delay the cellular response. This delay could be the result of the anomalies in the neuronal firing that precedes the cellular response to visual stimulation presented here.

We have shown an increase at low frequency retinal background noise, indicating a possible transient slow down disturbance in retinal neuron activity. Cannabis and alcohol are both psychoactive substances that modulate the synaptic release of neurotransmitters to exert their effects (Bossong and Niesink, 2010; Schwitzer et al., 2016a). The results of our study may therefore be explained by the potentiation of the effect of the two substances, alcohol and cannabis, on neurotransmission, particularly glutamatergic and dopaminergic neurotransmission. Glutamate is one of the principal excitatory neurotransmitters detected in the retina. It is involved in the vertical transmission of the retinal signal transmitted from the photoreceptors to the bipolar cells and subsequently to the ganglion cells (Schwitzer et al., 2016b). Furthermore, the depolarization and hyperpolarization processes at the origin of the retinal neuronal response, and measured using flash electroretinography, are directly influenced by glutamate concentrations. In our study, a modulation of the polarization of the retinal neurons responsible for the background retinal neuron activity disruption could be a result of the effect of exogenous cannabinoids on glutamatergic transmission. Indeed, by binding to presynaptic CB1 receptors, THC disrupts the regulation of glutamate release caused by endocannabinoids, leading to a synaptic excess of glutamate. This results in an excess of calcium at the postsynaptic level, leading to a state of cellular hyperexcitability (Bossong and Niesink, 2010; Schwitzer et al., 2016b; Schwitzer et al., 2015b; Colizzi et al., 2016). Regular alcohol consumption also causes a state of cellular hyperexcitability by inducing hypersensitivity of the postsynaptic NMDA glutamate receptors (Roberto and Varodayan, 2017; Burnett et al., 2016). Thus, the state of cellular hyperexcitability caused by the two substances could affect the pseudo-periodic stability of the neural response which could be reflected by the observed increase in retinal background noise. Like glutamate, dopamine is a neurotransmitter found in the cones and bipolar cells, the source of the ERG flicker response, and plays a crucial role in retinal processing of visual information (Schwitzer et al., 2015a; Bodis-Wollner, 2009; Ghilardi et al., 1989). Regular cannabis consumption may inhibit presynaptic dopamine release in the cones and bipolar cells, as this effect is found under synthetic exogenous cannabinoids (Yazulla, 2008). Regular alcohol consumption is also associated with a lower synaptic dopamine rate via a reduction in the number of DRD2 receptors (Engel and Jerlhag, 2014; Trantham-Davidson and Chandler, 2015; Thanos et al., 2001). A correlation between the reduction in retinal dopaminergic synaptic transmission and the increase in retinal background noise was shown by Bubl et al. in patients with an attention disorder with or without hyperactivity (ADHD) (Bubl et al., 2015). This effect is reversible under pharmacological dopaminergic treatment. This supports the hypothesis of a connection between the reduction in retinal dopaminergic synaptic transmission and the increase in retinal background noise (Forssberg et al., 2006; Volkow et al., 2012; Volkow et al., 2004). Thus, in our study, the increase in retinal background noise could also reflect a decline in synaptic dopamine release caused by the two substances.

Our study is faced with several methodological considerations and limitations that must be taken into account. A higher level of alcohol consumption is frequently observed in regular cannabis users versus healthy subjects (Meier et al., 2012). We have obtained results on a common effect, without being able to determine the role of each substance in the results obtained. This means that we cannot draw conclusions as to the isolated effect of each substance on background noise. Ideally, it would be pertinent to constitute a group of users of 'cannabis only' and a group of users of 'alcohol only' to evaluate precisely the impact of consumption of each of these toxic substances individually on retinal background noise. Constituting such groups is made difficult by the frequent co-occurrent consumption of these substances. Moreover, since deficits in cognitive functions are well known in cannabis users, it will be interesting to study correlations between alterations in retinal background noise and neuropsychological deficits in regular cannabis users.

Tobacco consumption is very common among frequent cannabis users, and tobacco is frequently used with cannabis to roll joints, particularly in France. Future studies should screen this bias with a control group including tobacco smokers. To our knowledge, the effect of nicotine administration on background noise has not been evaluated. Here, we did not find significant correlations between retinal background noise and Fagerström score in the two populations of cannabis users.

Our results suggest that an increase in retinal background noise is a marker of the potentiation of cannabis and alcohol neurotoxicity, but they do not indicate a potential threshold effect. Studying a threshold effect could determine the minimum quantity under which background noise is not affected and the maximum quantity above which it is no longer affected. This could make it possible to clarify whether background noise alterations begin from the experimental phase, or if they are only found with regular consumption or beyond a certain threshold of consumption of the two psychoactive substances.

Disclosures

All the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Contributors

All the authors contributed to write the manuscript, concurred with the submission and have approved the final manuscript.

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Review article

Cannabis use and human retina: The path for the study of brain synaptic transmission dysfunctions in cannabis users

Thomas Schwitzer[a, b], Raymund Schwan[a, b, c], Karine Angioi-Duprez[d], Laurence Lalanne[b, e], Anne Giersch[b], Vincent Laprevote[a, b, c]

[a] Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France
[b] INSERM U1114, Fédération de Médecine Translationnelle de Strasbourg, Département de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France
[c] Maison des Addictions, CHRU Nancy, Nancy, France
[d] Service d'Ophtalmologie, CHRU Nancy, Nancy, France
[e] Pôle de Psychiatrie et d'addictologie, Fédération de Médecine Translationnelle de Strasbourg, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France

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ABSTRACT

Owing to the difficulty of obtaining direct access to the functioning brain, new approaches are needed for the indirect exploration of brain disorders in neuroscience research. Due to its embryonic origin, the retina is part of the central nervous system and is well suited to the investigation of neurological functions in psychiatric and addictive disorders. In this review, we focus on cannabis use, which is a crucial public health challenge, since cannabis is one of the most widely used addictive drugs in industrialized countries. We first explain why studying retinal function is relevant when exploring the effects of cannabis use on brain function. Next, we describe both the retinal electrophysiological measurements and retinal dysfunctions observed after acute and regular cannabis use. We then discuss how these retinal dysfunctions may inform brain synaptic transmission abnormalities. Finally, we present various directions for future research on the neurotoxic effects of cannabis use.

1. Introduction

As cannabis is one of the most widely used drugs worldwide, its use is a major public health concern (Degenhardt et al., 2008). Cannabis use is known to be associated with several harmful effects on human health (Volkow et al., 2014). Among these, acute and regular cannabis use are linked to alterations in central nervous system (CNS) functioning (Broyd et al., 2016). For example, a decline in the main cognitive functions such as memory, attention, executive functions, speed of information processing and intelligence quotient (IQ) is observed after acute or regular cannabis use (Broyd et al., 2016; Meier et al., 2012). The neurotoxic impact of cannabis use on CNS functioning is mediated by the effect of exocannabinoids mainly delta-9 tetrahydrocannabinol (THC) on cannabinoid receptors mainly CB1- (Mechoulam and Hanus, 2000; Mechoulam and Parker, 2013). However, the precise mechanisms underlying these dysfunctions remain to be understood and are thus current research interests in neuroscience. Due to the difficulty of obtaining direct access to the functioning brain, new approaches are needed to study the neurological functions in an indirect manner.

In humans, the retina is endowed with a functional cannabinoid system, which implies that exocannabinoids should affect retinal functioning (Schwitzer et al., 2016b 2015b; Yazulla, 2008a). Cannabinoid receptors CB1 and CB2 are detected in the human retina (Porcella et al., 2000; Straiker et al., 1999a, b; Wei et al., 2009). CB1 receptors are expressed in the outer segments of photoreceptors, the inner plexiform layer, outer plexiform layer, inner nuclear layer, ganglion cell layer, and the retinal pigment epithelium. CB2 receptors are expressed in human retinal pigment epithelium cells. The two main endocannabinoid ligands -2-Arachidonoylglycerol (2-AG) and Anandamide are also detected in the human retina (Chen et al., 2005; Matias et al., 2006; Stamer et al., 2001). High levels of 2-AG are found in the retina whereas anandamide is expressed at a lower level. Several enzymes are involved in the regulation of the cellular level of retinal endocannabinoids and enable the degradation of cannabinoid ligands: fatty acid amide hydrolase (FAAH),

Corresponding author at: Psychotherapic Center of Nancy, 1, rue du Docteur Archambault, Laxou, F-54 521, France.
Email address: thomas.schwitzer@univ-lorraine.fr (T. Schwitzer)

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monoacylglycerol lipase (MGL), and cyclooxygenase-2 (COX-2) (Wang et al., 2011; Wei et al., 2009). FAAH is an integral membrane protein that is expressed in the human retina, especially in the retinal pigment epithelium (Wei et al., 2009). Recent findings also report a detection of COX-2 in the human retina (Wang et al., 2011).

Since endocannabinoids and cannabinoid receptors are detected in animal and human work, a potential role of exocannabinoids in retinal neurotransmission may be evoked (Laprevote et al., 2015; Schwitzer et al., 2015b; Yazulla, 2008b). For example, cannabinoid agonists are involved in dose-dependent reversible modulations of calcium, potassium, and chloride currents in bipolar, rod, cone, and ganglion cells (Fan and Yazulla, 2003, 2004, 2005, 2007; Lalonde et al., 2006; Opere et al., 2006; Straiker et al., 1999a, b; Straiker and Sullivan, 2003; Yazulla et al., 2000; Zhang et al., 2013). A direct effect of cannabinoids on enzymatic activity and transmitter release has also been described in the retina of animal species (Gawienowski et al., 1982; Middleton and Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Warrier and Wilson, 2007; Weber and Schlicker, 2001). In the bovine retina, THC leads to a dose-dependent modulation of monoamine oxydase activity (Gawienowski et al., 1982). In the isolated bovine retina, CB1 receptor agonists inhibit aspartate release, which is blocked by cannabinoid antagonists (Opere et al., 2006). In perfused guinea-pig retinal discs, dopamine and noradrenaline transmission release is inhibited by the activation of CB1 receptors, which is blocked by cannabinoid antagonists (Schlicker et al., 1996; Weber and Schlicker, 2001). Interestingly, the release of dopamine, GABA and glutamate can be modulated by cannabinoids (Middleton and Protti, 2011; Opere et al., 2006; Schlicker et al., 1996; Straiker and Sullivan, 2003; Warrier and Wilson, 2007; Weber and Schlicker, 2001). The retinal endocannabinoid system is also involved in other physiological neural mechanisms such as neural plasticity and neuroprotection (Schwitzer et al., 2016b).

The retina is a highly conducive site for the investigation of brain functioning in CNS and neuroscience research (Bernardin et al., 2017; Garcia-Martin et al., 2014; Laprevote et al., 2015; Lavoie et al., 2014c; London et al., 2013; Schwitzer et al., 2017b 2015a).The retina is an anatomical and developmental extension of the CNS due to its embryonic origin (Hoon et al., 2014). The retina and the brain are interconnected by the optic nerve, which is composed of the axons of ganglion cells, i.e. the final and more integrated retinal stage (Hoon et al., 2014). Retinal architecture, including retinal neurons and retinal microvasculature, shares similar features with these structures in the brain (Cheung et al., 2017). Retinal arterioles and venules and cerebral small vessels display similar size and regulatory mechanisms (Cheung et al., 2015, 2014; Patton et al., 2006, 2005). Retinopathy and retinal arteriovenous nicking are associated with an increasing risk of developing cerebral infraction and stroke. The retina is composed of layers of specialized neurons which are interconnected by synapses and under the influence of a complex neurotransmission system (Hoon et al., 2014). Retinal neurons are made up of a cell body, axons and dendrites, like the neurons in the brain. The axons of the retinal ganglion cells are myelinated when they leave the eye to form the optic nerve. This structure is particularly sensitive to inflammatory and immunological processes. For example, in multiple sclerosis, retinal architecture and functioning are altered, as observed with retinal imaging (optical coherence tomography: OCT) and functional (pattern electroretinogram) techniques, and vary with the course of the disease (Celesia et al., 1986; Holder et al., 2009; Sergott et al., 2007). The optic nerve converges at the optic tracts and the visual information is then relayed to the visual cortex. There is a significant connection between the retina and the brain which explains that pathological processes of the brain such as vascular, inflammatory, immunological, neurodegenerative processes and neurotransmission can also propagate in the retina (Ho et al., 2012; London et al., 2013). This can also explain why visual and retinal impairments are often observed in CNS diseases. As examples, in Alzheimer s disease (AD) or Parkinson s disease (PD), visual impairments often occur during disease evolution, suggesting alterations of the visual system (Ascaso et al., 2014; Bodis-Wollner et al., 1987; Bodis-Wollner and Yahr, 1978; Cronin Golomb et al., 1991; Crow et al., 2003; Garcia-Martin et al., 2014; Gottlob et al., 1987; Krasodomska et al., 2010; Langheinrich, 2000;; Lu et al., 2010; Moschos et al., 2012; Palmowski-Wolfe et al., 2006; Parisi et al., 2001; Peppe et al., 1995). In particular, recent results suggest that the architectural and functional properties of the retina are affected early in CNS diseases, implying that they may be early markers of CNS alterations (Lu et al., 2010; Moschos et al., 2012). Additionally, clinical studies support a link between visual and retinal impairments and clinical manifestations of CNS disorders. For example, in AD cognitive deficits such as loss of memory and attention are frequently associated with visual dysfunctions such as anomalies in contrast sensitivity, color discrimination, to name a few (Cronin Golomb et al., 1991; Crow et al., 2003; Moschos et al., 2012; Yamasaki et al., 2016). Abnormalities at the retinal level may participate to these deficits. Another finding in AD animal models and patients showed that beta amyloid (A) accumulation is detected in the retina and accompanied by degeneration of retinal ganglion cells (Koronyo-Hamaoui et al., 2011; La Morgia et al., 2016; Parthasarathy et al., 2015). Interestingly, the accumulation of A plaques occurs first in the retina and then in the brain. In immunological diseases, the retina can be affected before the brain and other CNS structures and retinal manifestations help us to reach a diagnosis, such as in several kinds of lymphoma (Buggage et al., 2001). Interestingly, such etiologies inflammation, neurodegeneration, vascular, immunological and neurotransmission processes are also suggested in the physiopathology of psychiatric disorders (Borroto-Escuela et al., 2016; Brites and Fernandes, 2015; Glausier and Lewis, 2017; Huang and Lin, 2015; Khandaker et al., 2015; Khandaker and Dantzer, 2016; Kim et al., 2016; Leboyer et al., 2016; Lopresti et al., 2014; Pasternak et al., 2015; Sanacora et al., 2003, 1999; Stuart et al., 2015).

Retinal function can be assessed by electrophysiological techniques known respectively as full-field electroretinogram (ffERG), pattern electroretinogram (PERG), multifocal ERG (mfERG) and electrooculogram (EOG) (Holder et al., 2010). ffERG, PERG and mfERG are objective and non-invasive techniques which record the electrical bio-potential evoked by retinal cells in response to a light stimulation. Each exam allows for the assessment of specific functional properties of retinal neurons (Holder et al., 2010). EOG measures the variation of electrical potentials between skin electrodes located in external and internal canthus and reflects retinal pigment epithelium and photoreceptor activity (Marmor et al., 2011). ffERG, PERG, mfERG and EOG have been evaluated in many neuropsychiatric disorders (Lavoie et al., 2014c; London et al., 2013; Schwitzer et al., 2015a). Although the study of the neurobiological effects of cannabis use only recently included the exploration of retinal function, several retinal dysfunctions have been observed with retinal electrophysiological techniques in cannabis users, after acute or regular use (Faure et al., 2016; Schwitzer et al., 2018 2017a 2016a; Zobor et al., 2015). It is thought that these retinal abnormalities reflect modulations in neurotransmission-signaling pathways and could thus reveal brain neurotransmission dysfunctions following acute or regular cannabis use.

This review first summarizes the arguments suggesting the retina is a relevant site to investigate brain neurotransmission anomalies in cannabis users. We then describe retinal electrophysiological measurements methods, as used in research with cannabis users. We also report on studies which have evaluated the impact of cannabis use

on retinal functioning. Based on the distribution of dopaminergic, glutamatergic and GABAergic retinal synaptic transmission and their role in retinal processing, we finally discuss the extent to which retinal dysfunctions detected in cannabis users could be markers of brain neurotransmission abnormalities.

2. The benefits provided by retinal processing measurements in neuroscience research

As already emphasized, the retina is an integral part of the CNS. The retina represents the first stage of visual processing when the light enters the eyes and thus represents an easy-to-access part of the CNS. The retinal function is not under the influence of high level cognitive functions attention for example such as when cortical visual processing is recorded. Retinal processing is a well-studied function (Hoon et al., 2014). Measurements of retinal processing are well standardized, allowing for good reproducibility (Holder et al., 2010). Electrophysiological tests may be used alone or coupled with another measure to accurately evaluate retinal functioning. Using these exams, the study of the retinal function is fast, inexpensive, and easy to conduct. It can be mobile and small. Retinal function anomalies evaluated by retinal electrophysiological measurements are associated with a series of neuropsychiatric disorders (Lavoie et al., 2014d; Schwitzer et al., 2017b 2015a; Silverstein and Rosen, 2015). Despite the fact that the majority of these studies are performed on small sample sizes and that the specificity of these markers should be confirmed, parameters extracted from retinal electrophysiological measurements may be candidates for use as functional indicators of neuropsychiatric disorders such as schizophrenia, bipolar and depressive disorder, neurodegenerative disorders, to name but a few. More specifically, ffERG may be used to examine neurotransmission abnormalities in neuropsychiatric disorders. Lavoie et al. (Lavoie et al., 2014a) showed that alterations in central dopamine and serotonin neurotransmission two neurotransmitters involved in the pathophysiology of neuropsychiatric and addictive disorders affected the ffERG responses in mice. ffERG may also provide early and specific functional markers of risk in developing neuropsychiatric disorders. In young non-affected and non-medicated offspring at high genetic risk of neuropsychiatric disorders, a specific electroretinographic anomaly was observed in the rod retinal response (Hébert et al., 2010). In this study, ffERG was performed in 29 high risk offspring having one parent affected by schizophrenia or bipolar disorder and 29 healthy control subjects. b-wave amplitude of the rod response in high risk offspring was significantly lower than in control subjects whereas the cone response showed no difference. This anomaly in retinal response was observed independently of parents diagnosis (schizophrenia or bipolar disorder) and was present in both the younger and older high risk offspring. Additionally, modifications of ffERG parameters, as shown by the alteration of the scotopic b-wave implicit time, were observed in mice after long term treatment by lithium, a mood stabilizer frequently used in bipolar disorder (Lavoie et al., 2015). This study shows that administration of lithium influences ffERG responses in mice and underlines the need to examine whether ffERG might provide relevant functional markers for pharmacotherapeutic evaluation.

Retinal electrophysiological measurements currently represent one of several tools available to neuroscience research to directly or indirectly study brain activity and accurately objectify brain dysfunctions in neuropsychiatric disorders in order to enhance understanding of brain function. Using the current standard toolbox in neuroscientific research, brain measurements are mainly represented by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Indirect physiological signals of CNS activity include electrodermal activity, heart rate variability, pupillary response, and blink-startle, amongst others. As with retinal electrophysiological measurements, many of these are inexpensive and easy to implement. In this section, the relevance of retinal electrophysiological measurements is discussed relative to fMRI and EEG, two measures of brain activity. EEG provides a measure of the brain's electrical activity and visual evoked potentials (VEP) allow the assessment of the visual system (Odom et al., 2010). VEP can be coupled with retinal electrophysiological measurements ffERG, PERG and mfERG to give a clearer picture of the visual system functioning. Interestingly, measurements of retinal activity using ffERG, PERG and mfERG and the measurements of cortical function with VEP share the same methodological characteristics (Bach et al., 2013; Holder et al., 2010; Odom et al., 2010). Both techniques can be performed with stimuli such as flashes or checkerboards, whose parameters such as intensity, contrast level, rate of stimulation, and size can be adapted to specific protocols (Bach et al., 2013; Holder et al., 2010; Odom et al., 2010). Moreover, the same stimulations can be used during simultaneous recording of retinal and visual cortical activity. Similarly, VEP and retinal electrophysiological measurements can be performed during visual tasks such as contrast sensitivity, or synchrony-asynchrony to observe how and where the visual system is affected. Since visual deficits are often associated with neuropsychiatric disorders, the combined measures of retinal electrophysiological measurements and VEP may provide information on the early and later localization of functional deficits within the visual system. Based on the hypothesis that early anomalies may be located in the retina, retinal electrophysiological measurements and VEP can be used in the follow up of visual system dysfunctions occurring in neuropsychiatric disorders. Besides electrophysiological techniques, MRI is a direct architectural brain measure whereas optic coherence tomography (OCT) is a direct anatomical retinal measure (Baghaie et al., 2015a; Hong et al., 2005). MRI and OCT do not provide information on function but can detect underlying morphological anomalies. Interestingly, MRI and OCT provide a continuous viewing of neuronal structure from retinal photoreceptors to visual cortical neurons. Above all, the optic nerve, which connects the retina and central structures in the brain, can be studied using both techniques. Adding functional or architectural retinal measurements to brain measures can offer the unique opportunity to study the CNS at two critical levels involved in visual processing, each of which can provide relevant information on the pathophysiological mechanisms involved in neuropsychiatric disorders. Additionally, eye and brain measures are based on the extraction of similar parameters. Amplitude and implicit time are derived from waveforms of VEP and retinal electrophysiological measurements (Holder et al., 2010; Odom et al., 2010). Morphological aspect, size and thickness are derived from structures observed with MRI and OCT (Baghaie et al., 2015b; Ives-Deliperi et al., 2013). Importantly, cortical and retinal electrophysiological measurements, as well as cortical and retinal imaging techniques, are currently seen as complementary measurements for detecting and monitoring eye and central visual deficits in neuro-ophthalmological disorders (Holder, 2001). Although this is an emerging field in neuroscience, using the coupled measures of retinal and cortical activity and/or retinal and cortical morphology enhances the powerfulness of exploration techniques in CNS disorders and may provide additional insights into diagnosis, prognosis, or therapeutic use to clinicians or researchers.

3. Measurements of retinal function

Several measurements of retinal functioning are currently available to neuroscience research. Each one of these techniques can provide information about the specific anomalies of the various retinal cell types. Since they allow for the precise evaluation of retinal cell functioning, they can be expected to provide specific markers of

synaptic transmission abnormalities, thereby helping us understand brain dysfunctions in cannabis users.

3.1. Experimental protocol

Retinal electrophysiological measurements are recorded in precise conditions in a specific room in which parameters such as obscurity and ambient light must be adjusted. In each of these conditions, the patients are placed facing a stimulator that emits visual stimuli, such as flashes, alternating black and white checkerboards, or an array of a rapidly changing sequence of black and white hexagons. Depending on the exams, the patient is placed at various distances from the screen. Electrical signals can be recorded on non-dilated and dilated pupils, generally with DTL (Dawson, Trick & Litzkow) or sclerocorneal electrodes, to name a few examples. The pupil s size is noted, when appropriate, before and after recordings and should remain systematically constant during the whole testing period. Ground and reference electrodes are usually attached to the forehead and external canthi. Before placing the electrodes, the skin is prepared and cleaned with pumice paste and alcohol to extract all deposits. There is usually an adaptation period before the exams are completed. Electrical signals are usually recorded simultaneously from both eyes, apart from mfERG. The electrical signals are then amplified with an amplifier and transmitted to a computer connected to the stimulator. Average retinal responses are first obtained from each eye and then the values of the parameters implicit time and amplitude are averaged over both eyes for analysis. The Guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) for EOG, PERG, ffERG nd mfERG help to standardize the methods (Bach et al., 2013; Hood et al., 2012; Marmor et al., 2011; McCulloch et al., 2015).

3.2. Full-field electroretinogram (ffERG)

The ffERG records the electric bio-potential evoked by the photoreceptors, known as rods and cones, and the ON-bipolar and Müller cells complex, in response to a light stimulation delivered as a flash (Holder et al., 2010). ffERG recordings are performed under scotopic and photopic conditions and are labelled dark- and light-adapted ffERG respectively, according to the flash luminance intensity used in candelas·s·m^2 (cd·s·m ^{2}) (McCulloch et al., 2015). They are dark-adapted for a period of 20 min before dark-adapted ffERG is recorded. They are light-adapted for 10 min to a light background set at 30 cd·m^2 (cd·m^2) managed by the stimulator before light-adapted ffERG is conducted. Recordings can be performed first in light condition and then in dark condition and reciprocally. At least 8 and 16 responses, for dark- and light-adapted ffERG respectively, are usually recorded. Each retinal response is labeled according to the strength of the flash in cd·s·m ^{2}. To assess the functioning of the rod and cone system separately, dark-adapted 0.01 ffERG and light-adapted 3.0 ffERG are performed respectively. Other dark-adapted and light adapted ffERG can also be used such as the mixed rod-cone response, also known as dark-adapted 3.0 ffERG. The two main components usually described on a typical ffERG are an electronegative component, a-wave, followed by an electropositive component, b-wave. The a-wave is not detected in the dark-adapted 0.01 ffERG response because it is masked by the b-wave. An a-wave is attributed to the retinal photoreceptors and a b-wave is attributed to the retinal bipolar cells, postsynaptic to photoreceptors. Two main parameters are derived from a- and b-waves, known by convention as the amplitude measured in microvolts (μV) and the implicit time measured in milliseconds (ms). The a-wave amplitude is measured from the baseline to the trough of the a-wave. The b-wave amplitude is measured from the trough of the a-wave to the peak of the b-wave. Implicit time denotes the time taken to reach the maximum a- and b-wave amplitudes (Holder et al., 2010; McCulloch et al., 2015). ffERG traces are represented in Fig. 1. ISCEV standard are available for ffERG (McCulloch et al., 2015).

3.3. Pattern electroretinogram (PERG)

The PERG records the central macular function of the retina, as well as the retinal ganglion cell response, using reversing black and white checkerboards (Holder et al., 2010). For example, to investigate the transient PERG according to international guidelines, a black and white contrast reversible checkerboard, with 0.8° check size, 93.3% contrast level, 100 cd·m^2 constant luminance white area, and 2 6 reversals per second (1 3 Hz) may be used. In the case of participants with refractive disorders, an appropriate optic correction is provided. At least 220 retinal responses are recorded for each participant, using constant ambient room-lighting to achieve the best signal-to-noise ratio. Two main components are usually described on a typical PERG trace: an electropositive component, P50, followed by an electronegative component, N95. N95 is believed to reflect the response of the retinal ganglion cells. P50 reflects the response of the retinal ganglion cells and macular photoreceptors and is used to evaluate the macular function. Two main parameters are derived from P50 and N95, known by convention as the amplitude measured in microvolts (μV) and the implicit time measured in milliseconds (ms). N95 amplitude is measured from the trough of the N95 to the peak of the P50. P50 amplitude is measured from the trough of the inconstant N35 or from the baseline to the peak of the P50. Peak time denotes the time taken to reach the maximum N95 and P50 amplitudes (Bach et al., 2013; Holder et al., 2010). A PERG trace is represented in Fig. 1. ISCEV standard are available for PERG (Bach et al., 2013).

3.4. Multifocal electroretinogram (mfERG)

The mfERG records the spatial properties of the retinal cone function (Hood et al., 2012). The mfERG measurements are performed in photopic conditions, generally with dilated pupils, but can also be performed with no eye dilatation. Each eye is usually tested monocularly, the other being occulted during the stimulation but mfERG can also be recorded in both eyes at the same time. The stimulus is composed of multiple hexagons gradually increasing in size from the center to the periphery of the screen (Holder et al., 2010). Each hexagon is illuminated pseudo-randomly by a flash stimulation and elicits a local response of the retinal cone system. The mfERG recordings allow for the evaluation of multiple local responses derived from each hexagon. Subjects are fully corrected optically for the viewing distance and asked to fixate on the central target. Any segments associated with blinks or eye movements are immediately rejected. At least 5000 responses are recorded for each eye of each participant with a level of noise maintained under 5 Kiloohm (K) to achieve the best signal-to-noise ratio. mfERG responses are averaged over five retinal regions: $<2^\circ$ (deg), 2 5 deg, 5 10 deg, 10 15 deg, and >15 deg. Three main components are usually described on a typical mfERG trace: a first negative wave called N1, followed by an electropositive component P1, and then a second negative wave N2. Two main parameters are derived from N1, P1 and N2, known by convention as the amplitude measured in microvolts (uV) and the implicit time measured in milliseconds (ms). The amplitude of N1 was measured from the baseline to the trough of N1. The amplitude of P1 and N2 are the trough-to-peak amplitude, measured respectively from the trough of N1 to the peak of P1 and from the peak of P1 to the trough of N2. Implicit time denotes the time taken to reach the maximum N1, P1 and N2 amplitudes. N1 results from the hyperpolarization of the

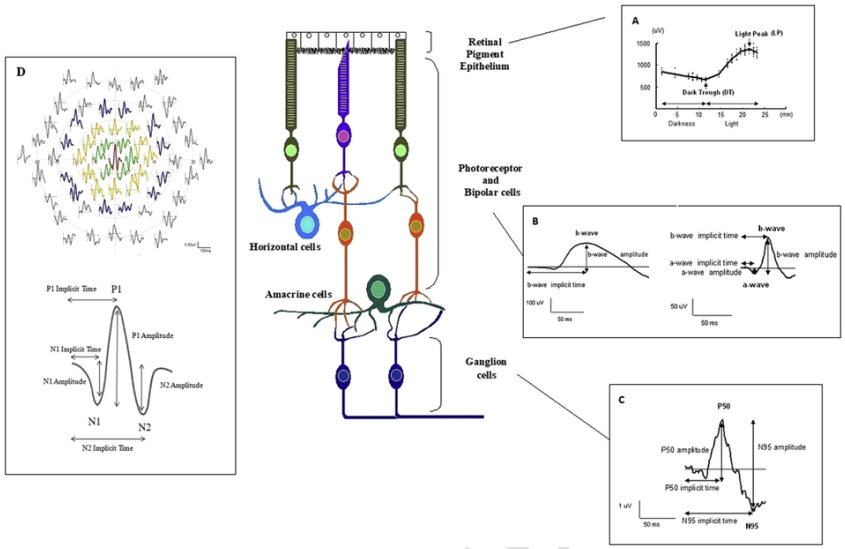

Fig. 1. Schematic representation of the retina with retinal electrophysiological measurements: A. Electrooculogram (EOG), B. Full-field Electroretinogram (ffERG), C. Pattern Electroretinogram (PERG), D. Multifocal Electroretinogram (mfERG).

OFF-bipolar cells and P1 results of the depolarization of ON-bipolar cells (Holder et al., 2010; Hood et al., 2012). mfERG traces are represented in Fig. 1. ISCEV standard are available for mfERG (Hood et al., 2012).

3.5. Electrooculogram (EOG)

The EOG allows to study the retinal pigment epithelium (RPE), and the interaction between the RPE and the photoreceptors via the variations of electrical potentials through the RPE (Holder et al., 2010; Marmor et al., 2011). Variations are measured by skin electrodes placed at the level of the internal and external canthus of the eyes (Arden and Constable, 2006). They correspond to an electrical potential between the front and the back of the eye and are known as standing potentials (Marmor et al., 2011). This potential mainly originates from the RPE and varies with the retinal illumination. It is recorded during a period of 15 20 min dark adaptation, and then during a 12 15 min period of light adaptation. The subject is asked to make 30-degree lateral eye movements alternately to the right and to the left, without moving the head. The eye movements are realized every 1 2 s for approximately 10 s every minute. Two parameters are derived from the EOG trace, namely the dark trough, which represents the trough of the curve in dark condition whose origin remains unclear, and the light peak, which represents the maximal peak in light condition and corresponds to the maximal depolarization of the basal membrane of the RPE. The ratio of the two gives the Arden ratio, normally greater than 180% and corresponding to the kinetics of apparition of the LP, reflecting the functioning of the basal membrane of the RPE. A decrease in the Arden ratio then supports anomalies in the depolarization of the basal membrane and photoreceptor activity, either by the failure of the signal to be transmitted by the rods to the internal layers of the retina and to the RPE, or by dysfunctions of the chloride channels at the level of the basal membrane (Holder et al., 2010; Marmor et al., 2011). Results obtained with EOG depend on the capacity of the subject to perform the eye saccades at a specific rate. If not performed correctly, the EOG will be abnormal. An EOG trace is represented in Fig. 1. ISCEV standards are available for EOG (Constable et al., 2017).

4. Retinal dysfunctions in cannabis users

The study of the retinal function in cannabis users is a recent field of investigation, but some results have nevertheless been observed after both acute and regular cannabis use. Our group investigated retinal function in a group of 53 cannabis users compared with 29 controls. In cannabis users vs. controls, we observed a delay in retinal response at two retinal levels: at the level of ON-bipolar cells of the cone system and at ganglion cell level (Schwitzer et al., 2017a 2018). The regular use of cannabis may alter the retinal function at two critical stages of retinal processing and involved in the vertical transmission of visual information in the retina, i.e. bipolar and ganglion cells, suggesting potential alterations in vision. No dysfunction was observed at the level of photoreceptor cells, suggesting that the phototransduction process is conserved. The main result concerns the delay observed in the ganglion cell response i.e. in the N95 implicit time measured with the PERG and calculated at approximatively 6 ms. This implies that visual information is delayed before leaving the retina through the optic nerve. Retinal ganglion cells form a complex neuronal network in the retina that features anatomical and functional properties similar to those of brain neurons, suggesting that they are a relevant site for the investigation of brain functioning in neuroscience research (Cheung et al., 2017; London et al., 2013; Schwitzer et al., 2017b). Retinal ganglion cells constitute the final and most integrated retinal stage which is located between visual phototransduction processing occurring in photoreceptors, and thalamic and cortical visual processing (Boycott and Wässle, 1999). The axons of ganglion cells, which transfer visual information to the brain, are myelinated nerve fibers (Shum et al., 2016). Ganglion cells provide response in the form of action potentials, as observed in brain neurons (Famiglietti and Kolb, 1976). Several kinds of ganglion

cells beta, alpha and gamma already initiate the parvocellular, magnocellular and koniocellular pathways, respectively, and most importantly display specific properties adapted to each pathway (Yoonessi and Yoonessi, 2011). The excitation and inhibition of ganglion cell response is mediated through feedback and feedforward mechanisms by several neurotransmitters, such as dopamine, serotonin, glutamate and -aminobutyric acid (GABA) (Hoon et al., 2014). Based on these similarities with brain transmission, retinal ganglion cell dysfunctions may help to provide an insight into brain abnormalities in CNS disorders (Fig. 2). However, electrophysiological tests should be coupled with other measurements such as molecular and genetic measures in order to validate and confirm pathophysiological hypotheses that may be evoked using retinal electrophysiological measurements.

We also found a delay of approximatively 1 ms in the ON-bipolar cell response a retinal stage that precedes the ganglion cell stage as shown by an increase in the b-wave implicit time of the ffERG photopic 3.0 (Schwitzer et al., 2018). Thus, visual information is already delayed before retinal ganglion cell processing but with smaller delays. The responses of retinal stages situated before ganglion cells photoreceptors and bipolar cells differ from ganglion cell response, since their responses to stimulation are a gradual variation of membrane potential (Baylor, 1996). Importantly, the depolarization and hyperpolarization of these cells occur mainly under the influence of glutamatergic signaling pathways, since glutamate is the key neurotransmitter involved in the transmission of vertical information within the retina (de Souza et al., 2013; Wu and Maple, 1998). In the case of cannabis use, anomalies in glutamatergic transmission might lie at the origin of these retinal dysfunctions since the pre-synaptic glutamate release is inhibited by the regular use of cannabis in central neurons (Bossong and Niesink, 2010). This inhibition is mediated through the blockade of CB1 receptors by exogenous cannabinoids such as THC, leading to an excess of post-synaptic influx of calcium. In the retina, cannabinoid agonists are involved in dose-dependent reversible modulation of several ionic currents calcium, potassium, chloride and in the direct regulation of glutamatergic transmission in bipolar and ganglion cells (Schwitzer et al., 2016b 2015b; Yazulla, 2008b). When we studied the sensitivity and specificity of these findings with a receiver operating characteristic (ROC) analysis, we observed that the N95 implicit time of the PERG (sensitivity = 79,2%, specificity = 79,3%) is a better marker than the b-wave implicit time of the ffERG photopic 3.0 (sensitivity = 71,7%, specificity = 69%), to correctly differentiate cannabis users from controls (Schwitzer et al., 2018).

In a single case, our group has also observed retinal dysfunctions after acute cannabis smoking (Schwitzer et al., 2016a). This observation was made possible by the need to conduct an annual ophthalmic evaluation in the context of a chloroquine intake for a systemic lupus erythematosus in a 47-year-old regular cannabis user. A complete ophthalmic evaluation including retinal electrophysiological measurements was performed twice, 30 min and 5 h after cannabis use. A large decrease of up to 48% in the ffERG a-wave amplitude was observed 30 min after cannabis intake for all scotopic responses compared with the responses 5 h after smoking. Acute use of cannabis may affect photoreceptor function. In another study using retinal electrophysiological measurements, no ffERG anomaly was found, either in a man suffering from a persistent perception disorder after cannabis use, or in four heavy cannabis users with no visual disturbance (Zobor et al., 2015). However, dysfunctions of the RPE were observed with EOG in the patient with perceptual hallucinations. These results should be viewed with caution (see also section 3.5) since an intrasubject reliability coefficient of 0.70 was reported by Seggie et al. (Seggie et al., 1991). This coefficient is lower compared to those reported with the ffERG (Hébert et al., 1999, 1995). In another single case observed in a 25-year-old man suffering from blurred vision of the right eye and who described a cannabis use of

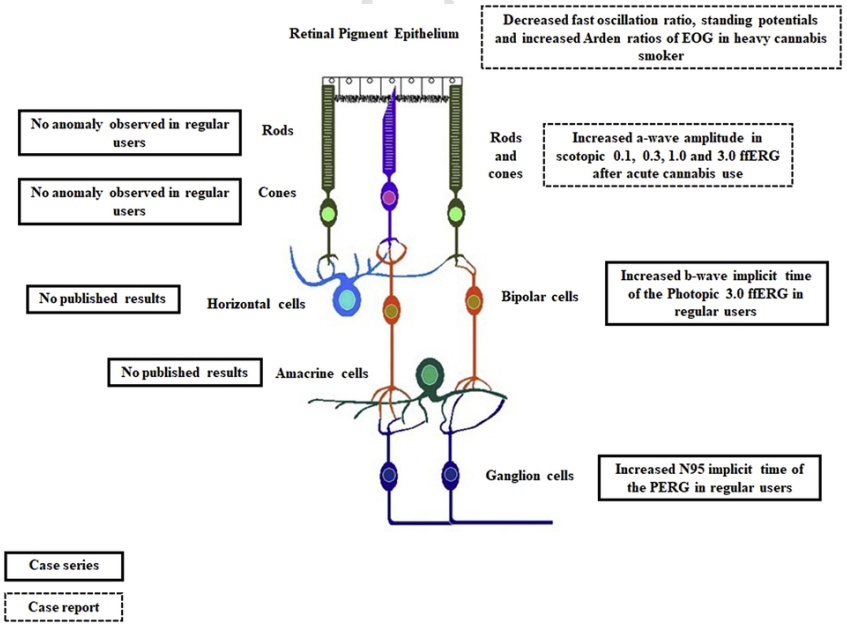

Fig. 2. Summary of retinal dysfunctions measured with electrophysiological techniques after acute and regular cannabis use and observed in case reports and case series.

approximatively 5 joints per day, multiple subretinal blebs were observed with OCT. These alterations were associated with a reduced light peak of the right eye measured with EOG, without ffERG anomaly (Faure et al., 2016). In this situation, intoxication due to cannabis was suspected. Interestingly, morphological anomalies observed with OCT gradually decreased with the reduction in cannabis use. Although there was no ffERG abnormality detected in this patient, retinal morphological changes were observed, suggesting that OCT measurements could be another avenue available for research in cannabis users.

We suppose that these retinal dysfunctions, observed after acute or regular cannabis use, might be viewed as retinal synaptic transmission anomalies and might provide insights into brain neurotransmission abnormalities in cannabis users.

5. Cannabis and retinal synaptic transmission

In the CNS, the neural modulation of synaptic transmission induced by exocannabinoids is mediated through the endocannabinoid system including cannabinoid receptors, ligands and enzymes (Mechoulam and Parker, 2013). This system is located in neurons involved in both excitatory and inhibitory regulation of central synaptic transmission (Mechoulam et al., 2007; Mechoulam and Hanus, 2000; Mechoulam and Parker, 2013; Pertwee et al., 2010). More precisely, it is located in neurons involved in GABAergic (Caballero-Florán et al., 2016; Szabo et al., 2002, 1998), glutamatergic (Auclair et al., 2000; Kim and Thayer, 2000; Robbe et al., 2001) and dopaminergic (Wu and French, 2000) synaptic transmission and mediates the effects of exocannabinoids on CNS functioning. As part of the CNS, the retina is endowed with complex neurotransmission-signaling pathways, including dopaminergic, glutamatergic and GABAergic pathways (Hoon et al., 2014). Interestingly, due to the anatomical distribution of these pathways throughout the retina and their role in retinal processing, we can assume that exocannabinoids modulate retinal processing and induce retinal dysfunctions, as observed with retinal electrophysiological measurements.

Dopamine is the main catecholamine in the retina of mammal species (Witkovsky, 2004) and dopaminergic retinal synaptic transmission may thus be modulated by exocannabinoids. Dopamine is synthesized from the L-amino acid tyrosine by the tyrosine hydroxylase (Reis et al., 2007) and acts on five G-coupled protein receptors divided into two subcategories: D1-class (D1-R) and D2-class (D2-R) receptors (Beaulieu and Gainetdinov, 2011; Frederick et al., 1982). Interestingly, D1-R are found in bipolar, ganglion and horizontal cells whereas D2-R are detected in horizontal, bipolar and photoreceptor cells (Nguyen-Legros et al., 1997). Dopamine is used by amacrine and interplexiform cells in most mammalian species (Dowling and Ehinger, 1978; Witkovsky, 2004) and plays a major role in light adaptation (Marshak, 2001). The role of dopamine in modulating electrophysiological signals in the human retina remains unclear (for a review on the role of dopamine in modulating retinal electrical activity recorded with ffERG, see Popova, 2014a). Many studies have investigated the role of dopamine neural transmission and the involvement of dopaminergic receptors in retinal functioning using electrophysiological measurements in a high number of non-mammalian and mammalian species. Many contradictory results exist concerning the dopamine effects on the retinal electrical activity evaluated with electrophysiological measurements as well as concerning the receptors involved in these effects (Popova, 2014a). Our results suggest ON-bipolar cell dysfunctions observed in the form of a delay, as shown by an increase in photopic b-wave implicit time under the influence of the regular use of cannabis (Schwitzer et al., 2018). The role of dopamine in modulating the ON and OFF pathways is well described but the precise mechanisms for the differential effects of dopamine agonists and antagonists remain unclear (Popova, 2014a). Modulation of the retinal dopaminergic pathway through agonists or antagonists leads to modifications in both amplitude and implicit time of the photopic b-wave, which depends on the receptors involved in the effects. At present, it is difficult to draw conclusions about the precise mechanisms of dopaminergic modulations underlying retinal dysfunctions found in cannabis users. The fact that we showed an implicit time anomaly rather than an amplitude variation suggests that the total amount of functional ON-bipolar cells involved in the retinal response is conserved but also that their functional properties are altered. This can be explained by the fact that the cannabis users recruited in our study were young consumers (18 35 years old). Similar measures will be performed in older consumers in order to show whether the total number of cells participating in the response will be decreased, as showed by decreased amplitude.

Glutamate an excitatory amino-acid is another key neurotransmitter involved in retinal processing and glutamatergic transmission could thus be altered by exocannabinoids. It is synthesized from glutamine by the aspartate aminotransferase (Brandon and Lam, 1983) and acts on five post-synaptic glutamatergic receptors detected in retinal synapses: kainate, AMPA and NMDA are ionotropic receptors whereas L-AP4 and ACPD are metabotropic receptors (Koulen, 1999). Glutamate is detected in photoreceptors, ganglion and bipolar cells, the three critical vertical stages of retinal processing (de Souza et al., 2013). NMDA receptors are mainly detected in bipolar and ganglion cells and L-AP4 receptors are found in photoreceptors and bipolar cells (Wu and Maple, 1998). The impact of exocannabinoids such as THC on glutamatergic transmission in CNS neurons has previously been described (Bossong and Niesink, 2010). This effect is mediated through CB1 pre-synaptic receptors and leads to apoptosis of the cell, suggesting a neurotoxic effect of the modulation of glutamatergic transmission by exocannabinoids on CNS neurons (Schwitzer et al., 2015b). In the bovine retina, the administration of 250 μm glutamate a glutamate stress model induced both a- and b-wave amplitude reductions (Januschowski et al., 2015). Using whole-cell voltage-clamp recordings in adult and young mice (P14 P21), exogenous cannabinoid agonists reduced the frequency of spontaneous postsynaptic currents in retinal ganglion cells (Middleton and Protti, 2011). Of interest, these results argue for a presynaptic action of cannabinoid agonists, as is observed in brain neurons, and are associated with a decrease in glutamate release (and GABA), suggesting the possible effect of exocannabinoids on retinal glutamatergic transmission (and GABAergic transmission).

Since GABAergic transmission is targeted by exocannabinoids and it plays a role in retinal processing, GABA could be another transmitter involved in retinal dysfunctions observed in cannabis users. GABA, an inhibitory neurotransmitter, is synthesized from glutamate by the glutamate decarboxylase (Brandon and Lam, 1983) and acts on ionotropic GABAa and GABAc receptors and on metabotropic GABAb receptors (Lukasiewicz and Shields, 1998). GABA is expressed in horizontal, amacrine, bipolar and ganglion cells in the retina of vertebrate species (Davanger et al., 1991; de Souza et al., 2013; Marc et al., 1995; Wu and Maple, 1998). GABAa and GABAb receptors are located in bipolar and ganglion cells and GABAc receptors in horizontal and bipolar cells (Lukasiewicz and Shields, 1998; Wu and Maple, 1998). The role of GABA acting through GABA receptors in regulating the ON and OFF responses in the retina, which are mediated by ON and OFF bipolar cells, is a matter of debate (Popova, 2014b). The summarized results suggest that GABA plays an inhibitory effect on both the ON and OFF retinal activity recorded with ffERG. This role of GABA signaling pathways depends on the type of the GABA receptors involved in the retinal response and is associated with various kinds of ffERG anomalies, namely alterations

of the b- (generated by the ON pathways) and D-wave (generated by the OFF pathways) amplitude and implicit time (Popova, 2014b). The ionotropic GABA receptors regulate chloride currents in bipolar cells but the precise effects on retinal activity of the ON and OFF bipolar cells remain to be determined. The GABAergic signaling pathways are involved in the ON-OFF asymmetry and sensitivity of the ffERG responses performed under various conditions of light adaptation in amphibian retina (Popova, 2014b). Further studies should establish whether GABA agonists and antagonists acting through ionotropic GABA receptors have the same role in human retina. Interestingly, horizontal cells could be a relevant focus for investigation of GABAergic transmission dysfunctions. According to Rangaswamy et al., the i-wave has an origin distal to the retinal ganglion cells, probably in the OFF-pathways, and could arise from horizontal cells (Rangaswamy et al., 2004). Although the origin of the i-wave is still under discussion, other authors also suggest that this wave reflects the ganglion cell function (Rosolen et al., 2004). The i-wave is a positive wave, posterior to the b-wave and observed in ffERG measurements in photopic conditions. In typical ffERG performed according to the ISCEV guidelines, the i-wave can be extracted from the photopic 3.0 ffERG. Amplitude and implicit time are derived from this wave.

In summary, the modulations of dopaminergic, glutamatergic and GABAergic transmission in animals are associated with several alterations of retinal electrophysiological parameters, as revealed by contradictory findings. Importantly, findings in animals cannot be translated to humans in the present form since animal physiology differs from the human variety. Also, it is crucial to consider that retinal responses recorded with electrophysiological measurements are under the influence of several neurotransmission signaling pathways and particularly depend on their reciprocal excitatory and inhibitory interactions. As a critical consequence, conclusions on modifications of an isolated retinal neurotransmission signaling pathways cannot be drawn. Future studies should focus on molecular analysis in order to directly link retinal dysfunctions with specific retinal neurotransmission abnormalities. To conclude, since exocannabinoids act on dopaminergic, glutamatergic and GABAergic retinal transmissions, retinal dysfunctions observed in cannabis users can be viewed as consequences of the modulation of these signaling pathways. However, the precise mechanisms underlying these dysfunctions needs to be accurately determined.

6. Future directions

Cannabis use is often associated with the use of other psychoactive substances, such as tobacco and alcohol (Agrawal et al., 2012; Meier et al., 2012). When assessing the impact of cannabis use on neurological functioning, it is difficult to draw conclusions on the direct and isolated impact of cannabis use without considering the interaction with tobacco and/or alcohol use. This is crucial since these drugs act on neural synaptic signaling pathways involved in the effects of cannabis. For example, another retinal measurement extracted from ffERG and called the retinal background noise may help to study the effect of cannabis and alcohol use on retinal synaptic transmission since an increase in the magnitude of the retinal background noise was observed in users with co-occurrent consumption of cannabis and alcohol (Lucas et al., 2018). Alcohol is known to be a modulator substance acting on dopaminergic, glutamatergic, and GABAergic signaling pathways (Miguel-Hidalgo, 2018) whereas tobacco is known to modulate dopaminergic, glutamatergic, GABAergic and nicotinic acetylcholinergic pathways (D Souza and Markou, 2013; Koukouli and Maskos, 2015; Pistillo et al., 2015). Thus, control groups of tobacco and alcohol users are needed to isolate the effects of each drug on central synaptic transmission. To date, acute administration of chewing gum containing 2 and 4 mg of nicotine 30 min before testing ffERG in adults who were nonsmokers induced a decrease in dark-adapted b-wave amplitude response as well as a decrease or an increase in light-adapted b-wave amplitude after chewing gum containing 4 mg of nicotine (depending on the protocol used: recording of dark- and light-adapted ffERG or only light-adapted ffERG, respectively) (Varghese et al., 2011). A recent study has evaluated the effect of cigarette smoking on structural and functional characteristics of the retina in 100 active smokers and 100 age- and sex-matched healthy passive smokers using mfERG and OCT (El-Shazly et al., 2018). P1 amplitudes of the mfERG in ring 1 were decreased and P1 implicit times in ring 1 were increased in active smokers vs passive smokers. Although this is an interesting result, it does not allow us to reach a conclusion on the effect of tobacco use vs no tobacco use on the retinal function. To our knowledge, the regular use of tobacco in humans on ffERG and PERG has not yet been investigated and could be of interest in future research. Similarly, the impact of acute or regular use of alcohol has not yet been evaluated and should be the goal of future studies in the field. Since the retina is endowed with molecular signaling pathways involved in the effects of these drugs on the CNS, we can expect retinal electrophysiological measurements to provide numerous markers of specific alterations of brain synaptic transmission.

Although the pathophysiology of psychiatric and addictive disorders is more complex than neurotransmission abnormalities, pharmacotherapy used in these disorders is currently based on these anomalies. There is substantial evidence that measurements of retinal function show markers of alterations in neurotransmission signaling pathways in neuropsychiatric and addictive disorders (Garcia-Martin et al., 2014; Lavoie et al., 2014c 2014a; Schwitzer et al., 2015a). For example, the retinal contrast processing obtained with steady-state PERG and consisting in the manipulation of the contrast levels of reversing checkerboards, is decreased in major depressive disorder (MDD) (Bubl et al., 2015, 2012, 2010). Other parameters derived from the transient PERG namely P50 and N95 amplitude as well as P50 implicit time were decreased in Parkinson s disease (Garcia-Martin et al., 2014). These two neuropsychiatric disorders are associated in an opposite way with alterations in dopaminergic transmission. Interestingly, different electrophysiological components extracted from different protocols of the same exam, the PERG, may vary in the same direction. These results suggest a potential way to study CNS dopaminergic dysfunctions (Schwitzer et al., 2016c). Further dopaminergic markers may be isolated from retinal function. Cocaine is a dopaminergic modulator substance which acts on the reward system. In a study in cocaine-dependent patients after cocaine withdrawal, approximately 50% of them showed a decrease in blue cone b-wave amplitude (Roy et al., 1997a, b). The ffERG of these patients was subsequently examined every 2 weeks for an 8-week period. Since no difference was observed over this period, this suggests that the reduced blue cone amplitude was stable in cocaine-dependent patients even during abstinence (Roy et al., 1997a, b). Interestingly, the reduced blue cone b-wave amplitude was significantly correlated with the cerebrospinal concentration of the dopamine metabolite homovanillic acid (HVA). Most importantly, HVA concentration was all the lowest that the blue cone amplitude was the lower (Roy et al., 2003). This reinforces the idea that the retinal signal is related to brain levels of dopamine, such as it was demonstrated in animals (Lavoie et al., 2014b). The retinal function may also provide markers of glutamatergic transmission. The transient PERG was altered in regular cannabis users, as shown by an increase in N95 implicit time (Schwitzer et al., 2017a 2018). Alterations in glutamatergic transmission may be at the origin of these abnormalities since exocannabinoids such as THC act on glutamatergic synaptic transmission (Bossong and Niesink, 2010) and glutamate is a key transmitter

involved in the vertical transmission of visual information in the retina (de Souza et al., 2013; Wu and Maple, 1998). Markers of other signaling pathways such as serotoninergic or noradrenergic pathways may be extracted from retinal functional measurements. In the study of Hébert et al. (Hébert et al., 2017), ffERG cone and rod luminance response functions were recorded in non-dilated eyes in 100 MDD patients, of whom 17 were drug free, along with 100 controls. In medicated MDD patients, a prolonged b-wave was observed at the cone level, the mixed rods/cones a-wave was reduced and a trend was observed for a reduced rod b-wave. Interestingly, medicated and nonmedicated patients share several similar retinal deficits suggesting that these retinal anomalies may be linked to the disease and not due to medication. Fountoulakis et al., (Fountoulakis et al., 2005) found correlations between ffERG parameters and psychometric assessments and symptoms occurring in MDD, such as General Assessment of Functioning Scale (GAF), or a number of atypical features or life events, although there were no a- or b-wave amplitude or implicit time differences between 50 MDD patients and 15 controls. Fornaro et al., (Fornaro et al., 2014) assessed, in 23 healthy volunteers aged between 22 and 35 years old, the impact of a single dose of 25 mg of agomelatine, a melatoninergic antidepressant, on ffERG. The retinal modification was a slight increase in the cone s b-wave amplitude and implicit time. Fornaro et al., (Fornaro et al., 2011) recorded ffERG in 20 patients with MDD and 20 healthy matched controls before and after 12 weeks of 60 mg duloxetine treatment, a Serotonin Norepinephrine Reuptake Inhibitor antidepressant. In patients suffering from MDD, a significant decrease in ffERG scotopic b-wave amplitude was observed from baseline to week 12 in depressed subjects achieving final response to an antidepressant therapy using duloxetine a serotonin-norepinephrine reuptake inhibitor. This result suggests a potential retinal marker of modifications in serotoninergic and noradrenergic pathways. Another study found that visual contrast sensitivity was significantly lower in MDD patients compared to controls based on the Landolt C visual contrast test, but no difference was found between groups using PERG and ffERG (Fam et al., 2013). In schizophrenia a mental disorder involving in part dopaminergic dysfunctions various ffERG abnormalities were observed in drug-naïve and treated patients, with a probable interaction between the effects of disease and pharmacotherapy mainly antipsychotics and anxiolytics on neurotransmission (Balogh et al., 2008; Hébert et al., 2015). As these treatments act on dopaminergic and serotoninergic signaling pathways for antipsychotics, and GABAergic pathways for anxiolytics, retinal dysfunctions may be viewed as modifications of synaptic transmission. In these studies, the main limitations concern the precise interpretation of these findings since both disease and medication intake are associated with modulation of several synaptic transmission pathways. In future research, it will be crucial to accurately evaluate the precise modifications of retinal function in response to the modulations of each neurotransmission signaling pathway. In other words, specific markers of the anomalies of each synaptic transmission pathway will be extracted from the retinal function.

Beside the parameters extracted from retinal electrophysiological measurements and evaluated in patients with neuropsychiatric and addictive disorders, numerous other retinal parameters will be evaluated to inform neurotransmission dysfunctions. Part of these parameters include well known indicators of retinal function, while others can be derived from electrophysiological measures of brain functioning. As an example, retinal oscillatory potentials, measured with ffERG under scotopic or photopic conditions, are markers of retinal amacrine cell functioning (Marmor et al., 1988a; Wachtmeister, 1998). The functioning of these cells is influenced by retinal dopaminergic transmission (Marmor et al., 1988b; Wachtmeister, 1998). Retinal oscillatory potentials may thus offer markers of dopaminergic transmission dysfunctions. The mfERG can also give interesting information in cannabis consumers. Since it examines the spatial properties of the cone system, it can be used to explore whether dysfunctions previously observed at the level of the ON-bipolar cells are localized in specific retinal areas or whether they are distributed over the whole retinal area. Other measurements can be derived from electrophysiological measurements of cortical functioning. As an example, neuronal background noise is a measure of a neuronal activity without stimulation, which is also known as non-stimulus-driven neural activity. One study evaluated the retinal background noise in attention deficit hyperactivity disorder (ADHD) (Bubl et al., 2013). In this study, the noise amplitude was significantly higher in patients with ADHD compared with controls and was significantly correlated with psychometric measures for ADHD, especially inattention. In this study, retinal background noise was viewed as a marker of dopaminergic dysfunctions.

In conclusion, there a large number of steps need to be taken before concluding on the relevance of these measurements to help us understand the precise effects of cannabinoids on brain functioning. Since the retina is an easy-to-access site for the investigation of brain disorders in neuropsychiatric and addictive disorders, measurements of retinal function may provide crucial information on the effects of cannabis use on brain synaptic transmission.

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Conflict of interest

None.

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