Cannabis, schizophrenia and cognition: the contribution of brain connectivity

Cannabis, esquizofrenia y cognición, aportes de la conectividad cerebral

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Abstract

The lack of consensus on the issue of whether the consumption of cannabis favors neurocognition among schizophrenia-diagnosed patients or not, plus methodological problems found in available evidence and the limitations of studies focused on diagnosis and treatment for positive symptoms are sufficient reason for designing new research proposals based on recent brain connectivity models. The objective of this paper is to review available literature databases, selected for neurocognition in cannabis-using schizophrenia patients and to analyze contributions made by functional connectivity studies. Cognitive impairment among schizophrenia patients is found even before the appearance of the first psychotic symptoms. Measuring cognitive function in these patients, techniques such as fMRI and EEG have found brain impairment. Furthermore, regarding schizophrenia-diagnosed patients who use cannabis, some studies have shown less deterioration among cognitive domains, which may apparently be related with one of its components (CBD). Measuring brain connectivity can be useful for clarifying neurophysiological mechanisms of cognition in marihuana-using schizophrenia patients. Cognitive decline is generalized in schizophrenia patients and is considered fundamental for disease physiopathology.

Keywords: Cannabis; Brain connectivity; EEG; Schizophrenia; Neurocognition.

Resumen

La falta de consenso sobre si el consumo de cannabis favorece la neurocognición en pacientes con diagnóstico de esquizofrenia consumidores de esta sustancia, más los problemas metodológicos encontrados en la evidencia disponible y las limitaciones de los estudios, los cuales se centran en el diagnóstico y tratamiento de los síntomas positivos, son elementos suficientes para diseñar nuevas propuestas de investigación desde los modelos recientes de conectividad cerebral. El objetivo de este trabajo es revisar la literatura disponible en las bases de datos seleccionadas sobre la neurocognición en pacientes con diagnóstico de esquizofrenia consumidores de cannabis y los aportes de los estudios de conectividad funcional. Alteraciones cognitivas en los pacientes con esquizofrenia, se evidencian incluso antes de la aparición de los primeros síntomas psicóticos; técnicas como RMFI y EEG han encontrado alteraciones en los cerebros de los pacientes con esquizofrenia. En los pacientes con esquizofrenia consumidores de cannabis, algunos estudios evidencian menores deterioros en los diferentes dominios cognitivos, que al parecer podían estar relacionados con uno de sus componentes, el CBD. La medición de la conectividad cerebral, puede ser útil para aclarar los mecanismos neurofisiológicos de la cognición en los pacientes con diagnóstico de esquizofrenia consumidores de cannabis.

Palabras clave: Cannabis; Conectividad cerebral; EEG; Esquizofrenia; Neurocognición.

Schizophrenia is defined as a serious mental disorder, characterized by fundamental and specific impairment in basic psychological processes such as thinking, perception and emotions, with consequences for behavior, the relationship with one's surroundings and with others (Arias, Szerman, Vega & Basurte, 2015). The disorder can be quite heterogeneous from the clinical point of view, both in its etiology and in its symptomatology, as well as in its neuropsychological characteristics (Alonso Solís & Pérez Sola, 2016). It constitutes 13% of the global burden of disease worldwide and is considered one of the main causes of disability; it is projected to be responsible for 15% of total morbidity by 2020 (Suarez-Escudero, 2014). Positive symptoms of schizophrenia are related to certain distortions or enhancements in some functions such as thinking and behavior, while negative symptoms correspond to a deficit or decrease of the same, and are thus also characterized by a group of cognitive symptoms. These symptoms of schizophrenia have a direct impact on occupational, family and social functioning, as well as on the patient's lifestyle and general health (Galderisi et al., 2013), with these in turn having a strong association with the clinical prognosis of the disease.

With regard to treatment, the focus has mainly been on the positive symptoms, although it has been shown in recent years that these are not the most relevant for the prognosis of the disease. Negative and cognitive symptoms have proved to be highly prevalent (García-Portilla & Bobes, 2013) and more related to the daily functioning and quality of life of people suffering from this disorder given that these negative symptoms persist despite the remission of positive symptoms, creating greater obstacles in daily life; furthermore, medication with proven efficacy for treatment is not yet available.

At the same time, cognitive impairment in patients with schizophrenia is considered a multifaceted and complex characteristic, independent of the psychotic episodes which occur. Such cognitive impairment is related to changes in brain activity in circuits supporting cognitive domains, such as attention, memory and language (Bagney Lifante, 2016). It is currently under investigation whether these impairments are specific or generalized, and if they compromise intellectual capacity (Gaviria Gómez, Queralt Salvat, Martínez Nadal, Novillo Jiménez & Salcedo Oliver, 2017).

In particular, it has been found that schizophrenia is principally comorbid with substance use disorders (Torrens, Mestre-Pintó, Montanari, Vicente & Domingo-Salvany, 2017). The most prevalent legal substances are tobacco and alcohol, while the most used illicit substance is cannabis, with figures between 22% and 40%; this level of consumption has been associated with greater psychotic episodes, an increase in positive symptoms, lower adherence to treatment programs and a worse prognosis (McLoughlin et al., 2014).

Nevertheless, the effects of this substance on neurocognitive functioning in this population are still unclear. Some studies have reported enhanced functioning in verbal memory, sustained attention, processing speed, executive functioning, general cognitive functioning and intellectual ability (Bugra et al., 2013; de la Serna et al., 2010; Ferraro et al., 2013); others have described below average cognitive performance in terms of memory and inhibitory response (González-Pinto et al., 2016; Lev-Ran, Segev, Braw & Levkovitz, 2012; Sánchez-Torres et al., 2013), and some have not found any differences (Núñez et al., 2016; Rabin, Zakzanis, Daskalakis & George, 2012; Wobrock et al., 2013). This could suggest that cannabis use can influence cognitive functions and that there are differences in the performance of cognitive domains in patients with psychotic disorders who use cannabis (Bogaty, Lee, Hickie & Hermens, 2018).

In this regard, one of the hypotheses suggests that cognitive dysfunction in schizophrenia may be the result of both functional and structural impairment in the brain due to the involvement of neural networks; clinicians and researchers have, in recent decades, focused on the possibility that this disorder is due to a pathology of the prefrontal cortex (Lozano & Acosta, 2009).

Along these lines, schizophrenia has been conceptualized as a connectivity disorder involving several brain circuits. Impaired connections in neural networks could explain the symptoms of schizophrenia and the related cognitive deficit (Orellana, Slachevsky & Silva, 2006). Weinberger and Berman (1996) proposed that deficient functioning of the frontal lobe, especially the deficit in working memory and other neuropsychological disorders, could be due to impairment in the circuit connecting the dorsolateral prefrontal cortex with the hippocampus. These contributions and the arrival of cognitive neuroscience methods such as neuroimaging and electroencephalography have aroused interest in characterizing brain connectivity in patients with schizophrenia and may help to resolve the contradictory findings related to cannabis use and cognition in these patients (Van Straaten & Stam, 2013).

This article aims to review the available literature on neurocognition in patients diagnosed with schizophrenia who use cannabis and the contributions of functional connectivity studies.

Method

A literature search was conducted using Medline, Pub med and PsychInfo without publication date restrictions. The English and Spanish search terms were "cannabis", "delta-9-tetrahydrocannabinol", "THC", "CBD" and "schizophrenia" cross-referenced with "cognition", "evaluation", "neuropsychological", "brain functioning", "neural

networks", "brain connectivity", "neuroimages", "EEG". Articles containing these search terms were included in this evidence-based review. Comments, letters to the editor and publishers were excluded.

Results

Neurocognitive profile of patients with schizophrenia

The literature reviewed reports evidence of cognitive impairment in the majority of patients with schizophrenia; this deterioration manifests itself during the development of the disorder, even before the onset of the first psychotic symptoms, leading to stable cognitive impairment in adult life which can range from dysfunctions at basic levels such as perception and attention to complex impairment in executive functioning and intellectual capacity. The findings do not seem to allow for a single profile as there is great heterogeneity among the results of the different studies although they do agree that there is general deterioration (Rebolleda Gil, 2017).

Regarding cognitive disorders in schizophrenia, the following have been described: generalized and attention deficit, processing speed deficit (Blanco, del Carmen Álvarez, Torres, Vázquez & Otero, 2018; Lahera, Ruiz, Brañas, Vicens & Orozco, 2017; Úbeda Cano et al., 2017; Toca, 2017); moderate cognitive impairment, changes in selective attention and cognitive flexibility (Blanco et al., 2018), in perceptual reasoning (Úbeda Cano et al., 2017), in sustained attention (Blanco et al., 2018; Toca, 2017); mild cognitive impairment and impairment of long-term declarative memory (Diaz Camargo, Delgado Sierra, Riano Garzon, Caballero Vargas & Moros Hernandez, 2017), alternating attention (Blanco et al., 2018; Diaz Camargo et al., 2017), working memory (Diaz Camargo et al., 2017; Úbeda Cano et al., 2017) and impairment of the executive function (Bilder et al., 2000; Diaz Camargo et al., 2017).

Furthermore, to measure cognitive function in patients with schizophrenia, the National Institute of Mental Health (NIMH) of the United States has standardized a neuropsychological battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), which measures seven neurocognitive domains: processing speed, sustained attention, working memory, problem solving, verbal learning, visual learning and social cognition (Green et al., 2004), all helping to better understand the cognitive profile of these patients (Kurebayashi & Otaki, 2018). Likewise, authors have found that MATRICS results have strong associations with functional connectivity, describing how cognitive performance improves with greater functional connectivity and deterioration increases with reduced connectivity and noting that the occipital lobe is the area most strongly associated with the cognitive domains proposed by the battery (Wu, Caprihan, Bustillo, Mayer & Calhoun, 2018).

Cannabis and schizophrenia - dual pathology model

Comorbidity with the use of psychoactive substances is commonly found in patients diagnosed with schizophrenia, making their prognosis difficult and increasing the risk of relapses and hospital readmissions due to the exacerbation of psychotic symptoms. Statistics show comorbidity rates between schizophrenia and substance use of between 30% and 66%. Among the substances most abused by these patients are alcohol, cannabis, tobacco and cocaine, with cannabis being the most prevalent (Torrens et al., 2017). Patients diagnosed with schizophrenia are more vulnerable to developing dependence on psychoactive substances, and drug use in this population is a phenomenon frequently observed in clinical practice (Szerman et al., 2016).

Drug induction has been proposed as a possible explanation for the comorbidity between severe mental illness and substance use disorders. In this process, the interaction of drugs with neurobiological systems (Alamo, López-Muñoz & Cuenca, 1999), expressed in a neurochemical deficit, is thought to influence the etiology of both drug use disorder and mental disorder (Extein & Gold, 1993). The reward system is involved in this deficit (Volkow & Fowler, 2000), and it has also been described as being associated with dopaminergic dysfunctions, in turn related to the negative symptoms of schizophrenia (Juckel et al., 2006) and may be related to a vulnerability to consumption (San, Arranz, & Martinez-Raga, 2007).

Likewise, self-medication theory suggests that patients diagnosed with schizophrenia consume psychoactive substances as a way of reducing the symptoms of the disease, specifically negative symptoms, dysphoria, depressive symptoms and some of the side effects of medication, such as extrapyramidal symptoms and sleep problems (Extein & Gold, 1993).

Along these lines, linked to neurochemical deficit and the possibility that it could be related to brain connectivity, Chambers et al. hypothesized that anomalies in the hippocampal/cortical function in schizophrenia impair the inhibitory projections of the hippocampus to the nucleus accumbens, resulting in reduced inhibitory control over dopamine-mediated functional hyperreactivity (Chambers, Krystal & Self, 2001).

In terms of the types of substances consumed by patients diagnosed with schizophrenia, psychostimulants and depressants have mainly been described. As regards depressant substances, we find alcohol, opiates, some psychoactive drugs such as benzodiazepines and cannabis (Szerman et al., 2016). These substances have the property of decreasing brain activity, which could reduce some symptoms, such as anxiety, in these patients.

With respect to cannabis use in this population, and even more so when the effects of the two main components of cannabis (the cannabidiol, or CBD, and delta-9-THC) are separated, it can be said that CBD has been promoted for its clinical benefits, proving effective in mitigating

the negative cognitive effects of THC (Yücel et al., 2016) and seemingly has opposite effects in THC-related brain activation (Colizzi & Bhattacharyya, 2017). In this regard, CBD treatment is described, in an animal model, as having safe and beneficial effects in the prevention of positive and cognitive symptoms of schizophrenia, and the involvement of the serotonergic system has been suggested in this effect (Peres et al., 2018). Conversely, there is sufficient evidence of the psychomimetic properties of delta-9-THC and its role in the worsening of psychotic symptoms (McLoughlin et al., 2014).

Cannabis, cognition and brain connectivity

As regards cognition, long-term cannabis use produces cognitive impairment with acute effects in which immediate but temporary changes are evident, as well as chronic effects which depend on habit, frequency, quantity and the user's basic cognitive ability. Findings in meta-analyses suggest poorer neurocognition in cannabis users, exacerbated with age, in functions such as processing speed, cognitive flexibility, sustained attention, learning and verbal memory; changes in the conceptual system, verbal fluency, motor inhibition and verbal working memory, where worse performance is described (Bogaty et al., 2018; Rabin, Zakzanis & George, 2011; Murat Yücel et al., 2012).

With regard to users of cannabis, more specifically THC, different acute effects generated by this substance on brain functioning have been described. These effects mainly generate a minor activation of the striatum, a structure which is responsible for the recovery of information, and hyperactivation of specific areas such as the hippocampal regions, which are involved in the coding of information and activation (Verdejo-García, 2011). Other areas involved are the frontal neocortical regions, responsible for executive functions –direction and control of directed behavior– as well as the ability to guide behavior towards specific objectives in the short and medium term, that is, motivation and the ability to inhibit inappropriate actions depending on context (Verdejo-García & Bechara, 2010).

In terms of brain connectivity, Böcker et al. (2010), using electroencephalography (EEG), found that after cannabis administration, users showed a dose-related decrease in theta band power, which has been associated with the activity in the mesial temporal lobe during working memory performance.

Similarly, EEG has also shown that cannabis use can interfere with the generation of gamma-band neuronal oscillations, a delta decrease and greater theta, beta and gamma power compared to controls, suggesting an increase in cortical activation at rest and a disinhibition of inhibitory functions that can disrupt cognitive processes, indicating that there are differences in cortical activity and connectivity between cannabis users and controls, which may be

related to possible cognitive disorders (Skosnik, Krishnan, D'Souza, Hetrick & O'Donnell, 2014).

On the other hand, functional magnetic resonance imaging (fMRI) studies have shown greater connectivity within the network in the orbitofrontal cortex (COF) in cannabis users compared to controls, both in studies at rest (Orr et al., 2013) and in task-based studies (Filbey & Yezhuvath, 2013). Behan et al. (2014) also found greater connectivity among adolescent cannabis users than controls in time series dependent on blood oxygen level (BOLD) in specific regions of interest (ROI), including the bilateral parietal lobe and cerebellum.

In their research differentiating cannabidiol (CBD) and delta-9-THC, Bhattacharyya et al. (2015) found that these compounds have opposite effects on functional connectivity among the dorsal striatum, the prefrontal cortex and the hippocampus. While delta-9-THC reduces frontostriatal connectivity, related to task performance, CBD improves it; the opposite effect was found on mediotemporal-prefrontal connectivity, which improved with delta-9-THC and was reduced with CBD.

Likewise, an fMRI study found evidence of attenuation of the blood oxygen level-dependent signal (BOLD) in the amygdala, the posterior and the anterior cingulate cortex (ACC) in response to the presentation of fearful faces, combined with a reduction in anxiety (Fusar-poli, 2014) in subjects to whom cannabidiol (CBD) was administered. This gives rise to the assumption that the impact of this substance on ACC activity can extend to the cognitive performance domain since it is considered that the modulation of ACC activity is the mechanism through which CBD affects brain connectivity during emotional processing (Fusar-Poli et al., 2010). The main target of CBD in terms of cognition is also suspected to be the ACC, which is understood to be an important relay station for cognitive control processes and as a region that integrates cognitive and emotional information.

On the other hand, the importance of analyzing the impact of genetics on cognitive impairment due to cannabis use has also been pointed out, since genetic variations can modulate the damage caused by this consumption in the central nervous system (Cosker et al., 2018). This is the case with some polymorphisms in genes such as AKT1 or COMT, which have also been described as influencing the risk of subsequent onset of psychosis in cannabis use (Radhakrishnan, Wilkinson & D'Souza, 2014).

It should be added that the impact on neurocognition may be modified by the COMT gene with varying acute and regular neurocognitive effects of cannabis, for example, modulating functions such as sustained attention; this gene found on chromosome 22q11.2 encodes the COMT enzyme, which is involved in the degradation of dopamine and other catecholamines, regulating the level of dopamine in the brain, particularly in the prefrontal cortex. As

a result of COMT polymorphism, there are differences in the activity of the COMT enzyme involving lower rates of dopamine in the prefrontal cortex (Cosker et al., 2018).

Brain connectivity in cannabis-using schizophrenia patients

Functional connectivity is defined as the temporal dependence of neuronal activity between anatomically separated brain regions, whose temporal dependence is related to structural connectivity, that is, to direct fascicular connections which can be studied using fMRI methods (Proal, E., Alvarez-Segura, M., de la Iglesia-Vayá, M., Martí-Bonmatí, L., Castellanos, F. X. & Spanish Resting State Network, 2011) and which are intended to mediate specialized cognitive performance. Intrinsic functional brain networks have been detected by means of functional neuroimaging techniques. One of these is the default network (DMN), which includes brain regions that are usually more activated during rest than during task performance. In relation to this network, hyperconnectivity has been detected in patients who use cannabis and are diagnosed with schizophrenia.

It has also been described that the DMN has negative relationships with other regions of the brain, such as the executive control network (ECN). As a result of these positive or negative relationships between different networks, functional connectivity is mooted, and in the case of the relationship between these two networks it has been mentioned that the effects of cannabis on the functional connectivity of the DMN and its interaction with the ECN may shed light on the effects of cannabis use on schizophrenia.

Similarly, an investigation found that when comparing cannabis-using patients diagnosed with schizophrenia with healthy controls before and after consuming THC, the differences found in the baseline state with respect to DMN and ECN connectivity were reversed, suggesting that THC consumption induces alterations in this connectivity, and that these are positively correlated with a better working memory (Whitfield-Gabrieli et al., 2018).

Regarding functional connectivity when at rest, a deterioration in connectivity between the nucleus accumbens (NAc) and prefrontal cortical regions was found in cannabis-using patients diagnosed with schizophrenia. These areas are involved in the processing of reward. Decreased connectivity between the NAc and the dorsolateral prefrontal cortex, involved in the exercise of executive control modulation, was also found (Liemburg et al., 2012).

Other authors, in contrast, have found significant improvements in connectivity between the NAc components and the reward circuit in schizophrenics who smoke cannabis. These areas are frequently described as hypo-connected in patients compared to controls, and this connectivity is found to be induced by cannabis and THC (Oleson & Cheer, 2012).

Cannabis use has thus been associated with altered sensory activation and neural oscillation; however, it is not clear which component of cannabis is responsible for these effects, or if they are mediated by CB1 receptors, although it has been found that the endocannabinoid system mediates theta oscillations relevant to perception and cognition (Skosnik et al., 2018). A relationship between the interruption of gamma-band neuronal oscillations and the phenomena relevant to cannabinoid-induced psychosis has also been found (Cortes-Briones et al., 2015).

Discussion

While some studies show that cannabis can have negative effects in patients with schizophrenia (Arias-Horcajadas, 2007; Large & Nielssen, 2013; Verdejo-García, 2011), others show that it may be a factor in the preservation of cognitive functions (Rabin et al., 2011; Suero-García, Martín-Banderas & Holgado, 2015). We may speculate that schizophrenia patients who benefit from cannabis use belong to a subset of subjects; nevertheless, the effects of this substance on neurocognitive functioning in this population are not yet clear (Rabin et al., 2011).

This lack of clarity is a result of the inconsistent results reported by the studies. Some have revealed cognitive impairment (Ringen et al., 2010) and gray matter deficits, as well as enlargement of the lateral ventricle and brain abnormalities (Bugra et al., 2013; Rais et al., 2010) in cannabis users presenting a first psychotic episode; other authors have suggested that cannabis use in subjects with first psychotic episode is associated with better cognitive ability, better functioning and fewer brain abnormalities (Ferraro et al., 2013). In addition to these conflicting results, cannabis has been shown to have a harmful effect on cognition in both animal models (Zanettini, 2011) and healthy individuals (Meier et al., 2012). Likewise, greater vulnerability to the detrimental effect of cannabis on cognition has been found in patients with schizophrenia compared to healthy controls, specifically in the domains of memory and learning.

Given the cognitive differences in cannabis-using schizophrenic patients in comparison to non-users, Rabin, Zakzanis and George warn that divergent findings are the result of methodological problems (Rabin et al., 2011) related to the samples, the groups compared, the inclusion and exclusion criteria, factors associated with cannabis use such as frequency, dose, age of onset, time of last intake; as well as the moment at which the measurement of the neurocognitive domains is made (Bogaty et al., 2018). To this must be added the need to also consider the genetic component of some polymorphisms in genes such as COMT, which has an impact on neurocognition, modulating, for example, functions such as sustained attention (Cosker et al., 2018).

Similarly, other authors propose the option of collecting data at the genetic and cerebral levels, since these aspects

could be modulating the results obtained, as shown in their research, and also environmental and psychological variables (Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2019). In order to obtain more solid conclusions, García et al. recommend greater uniformity in the type of patients with respect to the type of psychosis, as well as assessment methods and the choice of variables to be taken into account in future research, which should preferably be longitudinal in order to observe changes in neurocognitive functioning in relation to cannabis use profiles (García Álvarez, Gomar, García-Portilla & Bobes, 2019).

Notwithstanding the above and the attempts to ensure greater methodological rigor, it is very likely that the data on the relationship between cannabis use and cognition remain conflicting since cognitive deficits are central symptoms of schizophrenia. This implies that research studies should include variables such as genetics, epigenetics and neural networks. With regard to the former, it has been suggested that the effects shared between this and the family environment are influential in the development of brain structure and the use of cannabis. In a large sample of twins/normal siblings, Pagliaccio et al. (2015) reported that cannabis exposure has been associated with small abnormal subcortical structures resulting from cannabis abuse.

Conclusions

In relation to brain connectivity, the available evidence indicates that mental disorders, more specifically those in schizophrenia, are associated with subtle abnormalities distributed throughout the brain (Bora, Fornito, Pantelis & Yücel, 2012; Fornito, Yoon, Zalesky, Bullmore & Carter, 2011), which implies that they arise from disordered interactions between the activated neural connections. Consequently, hopes for the understanding of psychopathology and the development of more specific interventions in psychiatry are currently placed in research that attempts to map the molecular determinants and clinical correlates of neural circuit abnormalities in mental disorders (Meyer-Lindenberg, 2010).

Thus, neurophysiological studies with quantitative electroencephalography and functional magnetic resonance imaging (fMRI) could help delineate the brain mechanisms of schizophrenia, while also contributing to biological validation in relation to functional processes associated with variations in cognition in cannabis-using patients of schizophrenia. However, in delineating these mechanisms, the impact of genetics on cognitive impairment should be taken into account because this could help elucidate the elements that link cannabis, psychosis and cognitive impairment which is present in psychosis (Cosker et al., 2018).

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