# Cannabis use and cognitive impairment in schizophrenia and first-episode psychosis

## *Consumo de cannabis y alteraciones cognitivas en esquizofrenia y primeros episodios psicóticos*

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Cannabis is used extensively worldwide, although its effects on the brain and cognition remain controversial (Block et al., 2000; Jager et al., 2007; Martin-Santos et al., 2010). The use of this substance has been linked to a greater risk of psychosis (Casajuana Kögel, López-Pelayo, Balcells-Olivero, Colom & Gual, 2018; Gage, Hickman, & Zammit, 2016; Koskinen, Lohonen, Koponen, Isohanni, & Miettunen, 2010; López Pelayo, de Miquel Montagut, Casajuana Kögel & Balcells Oliveró, 2018; van Os et al., 2002), and it has also been observed with greater frequency among patients with schizophrenia than in the general population (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006). The prevalence rate of cannabis use disorders is below 10% in the general population (Moore et al., 2007) but rises to 27.1% among patients with schizophrenia (Koskinen et al., 2010). Moreover, in the case of cannabis use in first-episode psychosis (FEP), these figures are even higher, with rates up to 65.7% reported (Schimmelmann et al., 2012).

Cognitive impairments and functional impairments secondary to them develop early in schizophrenia and remain stable and persistent throughout the development of the disorder (Heaton et al., 2001). In addition, premorbid cannabis use has been associated with more symptoms and worse functioning in patients with schizophrenia spectrum disorders (Ringen et al., 2016). However, earlier studies of how cannabis use affects patients with schizophrenia at the cognitive level are varied (Potvin, Stavro, & Pelletier, 2012).

### The impact of cannabis use

Although different studies have observed a positive association between cannabis use (history of cannabis use or current consumption) and cognition, both in patients with schizophrenia (DeRosse, Kaplan, Burdick, Lencz, & Malhotra, 2010; Helle, Loberg, Gjestad, Schnakenberg Martin, & Lysaker, 2017; Meijer et al., 2012; Yucel et al., 2012) and in first-episode psychosis (Cunha et al., 2013; de la Serna et al., 2010; Leeson, Harrison, Ron, Barnes, & Joyce, 2012; Rodriguez-Sanchez et al., 2010; Yucel et al., 2012), such better performance has not always been found in all areas assessed (Bahorik et al., 2014; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009). Furthermore, many of these positive results come from studies which included patients with a lifetime history of use rather than current or recent users (Yucel et al., 2012), while other studies have yielded a relationship between a history of cannabis use or current consumption and worse cognitive performance in patients with psychosis (Waterreus, Badcock, Di Prinzio, Martin-Iverson, & Morgan, 2017), schizophrenia (Meijer et al., 2012; Sanchez-Torres et al., 2013) and FEP (Gonzalez-Pinto et al., 2016), although in the latter case, this worse per-

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formance has been related to the intensity of use during the previous year (Nunez et al., 2016) or with an absence of a family history of psychosis (Gonzalez-Pinto et al., 2016). Similarly, it has been reported that cognitive functions improve in cannabis dependent patients with schizophrenia and FEPs on cessation (Rabin et al., 2017; Setien-Suero et al., 2018), while such improvements are less notable in healthy controls (Rabin et al., 2017). In other cases, the differences observed disappear once certain confounding variables such as age, age of onset of illness, premorbid IQ or socioeconomic factors are controlled for (Leeson et al., 2012; Power et al., 2015). Finally, in a smaller number of studies, cognitive differences in terms of cannabis use in this type of patient were not found (Bugra et al., 2013).

In addition to all the above, better or worse cognitive performance in cannabis users has been related to the diagnostic picture; thus cognitive performance in purer psychoses with less interference from affective psychopathology seem to be better (Hanna et al., 2016) or at least not worse (Waterreus et al., 2017) than in those with other types of psychosis, where the affective component is fundamental. Similarly, besides different patient profiles, different cannabis user profiles could also result in cognitive performance variation (Schnakenberg Martin et al., 2016).

## Cognitive variables assessed

Neurocognitive deficits among patients with schizophrenia have been widely documented and are considered one of its central features (Elvevag & Goldberg, 2000; Green, Kern, & Heaton, 2004). They appear to be present from the first episode of psychosis and even in first-degree relatives of patients with schizophrenia without evidence of psychotic symptoms (Asarnow et al., 2002), suggesting that certain cognitive impairments could be components of a genetic vulnerability to schizophrenia.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative of the National Institute of Mental Health (NIMH) includes seven cognitive domains as being characteristic of schizophrenia: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Kern et al., 2008; Nuechterlein et al., 2008). In research on cannabis and cognition in schizophrenia, different studies have assessed neurocognitive functions such as attention/vigilance, memory, verbal learning, processing speed, executive functions, verbal fluency, etc., as well as also others such as social cognition, emotional recognition or theory of mind. However, the tests used to measure the different cognitive variables have been diverse, and very few studies have used MATRICS (Bahorik et al., 2014), as recommended by the NIMH.

## Neurocognitive variables

Regarding attention capacity in patients with schizophrenia who use cannabis, the results are controversial. Some studies observe greater attention capacity in more frequent users (Schnell et al., 2009), while others report that patients who use cannabis but had not done so in the previous 30 days performed better (Bahorik et al., 2014). Likewise, lower IQ in cannabis users predicts worse attentional performance in healthy controls but not in patients with schizophrenia or their siblings (Sanchez-Torres et al., 2013). In FEPs, patients with a history of cannabis use or those using cannabis before the onset of the disorder suffered fewer attention impairments compared to those without a history of cannabis use (Cunha et al., 2013; Rodriguez-Sanchez et al., 2010). Nevertheless, it has also been observed that heavy users in the year prior to the assessment had worse cognitive performance than non-users or those with a weaker pattern of use (Nunez et al., 2016).

The memory types assessed in the various studies have been diverse: visual (Sanchez-Torres et al., 2013; Yucel et al., 2012), verbal (Rabin et al., 2017; Sanchez-Torres et al., 2013; Schnell et al., 2009; Setien-Suero et al., 2018), episodic (Mallet, Ramoz, Le Strat, Gorwood, & Dubertret, 2017), immediate (Nunez et al., 2016), working (Gonzalez-Pinto et al., 2016; Meijer et al., 2012; Menendez-Miranda et al., 2019; Nunez et al., 2016; Schnell et al., 2009; Yucel et al., 2012) or long-term memory (Nunez et al., 2016), and their results are not conclusive. Patients with schizophrenia and a history of cannabis use have, in some cases, shown better knowledge acquisition (Meijer et al., 2012) and better performance in memory tasks (DeRosse et al., 2010; Menendez-Miranda et al., 2019); even patients who had been heavy users before the onset of the disease seemed to show better episodic memory (Mallet et al., 2017). However, a lifetime history of cannabis use among siblings of patients with schizophrenia has been linked to a negative effect on declarative memory, both visual and verbal (Sanchez-Torres et al., 2013). Furthermore, current use of cannabis in patients with schizophrenia has been associated in some studies with worse working memory performance (Meijer et al., 2012), while other studies link higher consumption to better performance (Schnell et al., 2009). Others find that verbal memory improves when patients with schizophrenia quit cannabis, but not when healthy controls do so (Rabin et al., 2017). In FEPs, both with and without a history of cannabis use, worse memory scores have been observed than in healthy controls (de la Serna et al., 2010). It has also been observed in cases of FEP that heavy cannabis users in the previous year showed impairments in immediate, short-term and long-term verbal memory compared to non-users (Nunez et al., 2016), although one study observes this relationship between cannabis use and worse verbal memory only in FEP cases without a family history of psychosis, but not in those who with one. Likewise, FEP

sufferers who stop cannabis use have displayed improved verbal memory (Setien-Suero et al., 2018). In terms of working memory, FEPs with cannabis use seem to perform worse (Gonzalez-Pinto et al., 2016).

Research on verbal learning in patients with schizophrenia again yields contradictory results. Patients with schizophrenia and a history of cannabis use perform better in verbal learning compared to patients without a history of use (DeRosse et al., 2010), while at the same time current cannabis use is associated with worse performance in immediate verbal learning (Meijer et al., 2012). In FEPs, both patients with a history of cannabis use and those without it have lower verbal learning scores than healthy controls (de la Serna et al., 2010).

Lifetime cannabis use in people with psychotic disorders (Power et al., 2015) or schizophrenia (Menendez-Miranda et al., 2019) has also been linked to processing speed, but results again diverge; while some studies observe better performance (DeRosse et al., 2010; Rabin, Zakzanis, Daskalakis, & George, 2013), others find the opposite (Meijer et al., 2012). However, once certain confounding variables are controlled for (age, age of onset of illness, premorbid IQ, and socioeconomic factors) the association between cannabis and processing speed disappears (Power et al., 2015). Likewise, in siblings of patients with schizophrenia, a history of lifetime cannabis use seems to have a negative effect on processing speed, but this is not the case in healthy controls, unless tobacco use is included. i.e., a negative relationship is observed between lifetime use of cannabis and smoking and processing speed in healthy controls (Sanchez-Torres et al., 2013). In FEP, heavy cannabis use during the previous year is associated with slower processing speed (Nunez et al., 2016).

Finally, executive functions have been positively associated with the use of cannabis in patients with schizophrenia (Helle et al., 2017; Schnell et al., 2009). In FEP cases, a history of cannabis use before the onset of the disorder has been linked to better executive function performance (Cunha et al., 2013; Rodriguez-Sanchez et al., 2010; Yucel et al., 2012). However, a variable that again appears to mediate is family history of psychosis, given that FEPs with cannabis use but no family history of psychosis perform worse in executive functions, while those with a family history of psychosis did better (Gonzalez-Pinto et al., 2016).

## Social cognition

With regard to the relationship between cannabis use and social cognition in schizophrenia patients, the data are again contradictory. While some observe better recognition of facial emotions and identity in patients with schizophrenia and a history of cannabis use (Meijer et al., 2012), others find worse emotional recognition (Helle et al., 2017) and social cognition (Sanchez-Torres et al., 2013) as well as better performance when cannabis use ceases 30 days before assessment. In addition, others find no relationship between cannabis use and theory of the mind (Helle et al., 2017).

## Possible explanations for the inconsistency in results

Various hypotheses have been posited to explain the observed results. It may be the case that patients who use cannabis constitute a subgroup of patients with better premorbid adjustment and better premorbid prefrontal cognitive functions (Rodriguez-Sanchez et al., 2010). Perhaps the etiological process of the psychotic picture of these patients is different, with FEPs who use cannabis and develop psychosis representing a group of patients with less damage at the neurodevelopmental level, and, therefore, a greater cognitive reserve than other psychotic patients (Cunha et al., 2013). The use of cannabis could trigger initial psychosis among people who may otherwise have had a good prognosis with later onset or even without developing the symptoms due to the toxic action of cannabis rather than the intrinsically greater severity of the disease (Leeson et al., 2012). It has also been suggested that better cognitive function in patients with schizophrenia who use cannabis could reflect less vulnerability to psychosis (higher level of functioning and cognitive ability) compared to other patients with schizophrenia (Schnell et al., 2009). An attempt has also been made to explain the fact that patients with schizophrenia and a history of cannabis use have better cognitive performance on the basis of greater social cognition, but results do not support this hypothesis (Helle et al., 2017). Likewise, it has been suggested that the different pattern of associations between the use of cannabis and cognitive performance in patients with schizophrenia in comparison to siblings of patients or healthy controls could already be explained by the negative impact produced by the disorder itself (Sanchez-Torres et al., 2013). Finally, it seems that the cannabis dose used may be a variable influencing the differences found at the cognitive level (Nunez et al., 2016).

## Conclusions

The different studies of psychosis, cannabis and cognition differ in aspects that may be relevant and connected to the differences observed in the results. Thus, there are studies which have focused on psychosis in general, including affective psychoses, while others have focused specifically on schizophrenia or on first psychotic episodes. Nevertheless, it is well known that the differential characteristics of the clinical pictures involved should be studied in isolation so that results can be verified and replicated. Similarly, some studies observe differences depending on

whether or not patients have a family history of psychosis, which therefore becomes another variable to be taken into account when replicating the different results. Likewise, on the subject of cannabis use, some studies focusing on a history of lifetime use may include subjects who have used it only at relatively specific moments or who have not used it for years, while others focus on current consumption, which may involve different patterns of use (mild, moderate, severe) with different consequences. Other aspects of this use which are also important to consider with respect to the time of onset of schizophrenia are whether it preceded the disease, whether it continued during the first years or whether it occurred uninterruptedly. Finally, on the subject of cognitive impairments, assessments have also diverged, not only regarding the cognitive variables measured or in terms of the number of areas included, but also in the tests used. Although there is a consensus in the assessment of cognition among patients with schizophrenia through MATRICS, there are few studies that use this test. Therefore, before firm conclusions about the obtained results can be reached, uniformity is required in the type of patients included, as well as in the variables to be assessed and the way to measure them. At the same time it would be very important to carry out longitudinal studies to see the changes in the cognitive variables depending on the pattern of concurrent or prior use and include all the confounding variables which may be intervening.

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## Conflict of interests

The authors declare no conflict of interest.

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