Review

Cannabis-Induced Fregoli Syndrome, a case report and literature review

Giovan Battista Ivan Polichetti

Department of Mental Health and Addiction, Local Health Trust of Romagna, Cesena, Italy

SUMMARY

Objective

Fregoli syndrome is already very rare in itself, and even rarer are those syndromes due to a general medical condition or induced by substances. Since a cannabis-induced Fregoli syndrome has never been described, and the author of this article has diagnosed one, not having obtained the patient's consent to publish his story, he presented it as a starting point, anonymously, taking advantage of the opportunity to write a systematic and complete review on the subject, in an attempt to provide a contribution to the study of this phenomenon but above all to invite scientists to search for other possible cases caused by cannabis.

Methods

This work could constitute an interesting review on the psychiatric and neurological nature of the syndrome, but insinuating among researchers who are interested in addictions, the doubt that even a substance of abuse can induce this syndrome.

Results

Few studies have examined samples of people with cannabis-induced psychotic symptoms; none of these has investigated the cannabis liability, in particular; the author was able to find a particular case, certainly induced by cannabis. All the available studies and sources have been ordered in such a way as to consider all the possible conditions in which Fregoli syndrome has been observed, studied and then published, regardless of the exotoxic etiology, which has been therefore considered in more detail.

Conclusions

only two articles considered the possibility of an exotoxic etiology in Fregoli syndrome – however excluding it – and only one case report has general characteristics that are comparable to those that will be presented in the current paper, even if it refers to ecstasy and not to cannabis.

Key words: Cannabis-induced Fregoli syndrome, cannabis-induced psychosis, Fregoli syndrome, Capgras syndrome, delusional misidentification syndromes.

Giovan Battista Ivan Polichetti
E-mail: giovanbattista.polichetti@auslromagna.it

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Introduction

Fregoli syndrome is one of the so called "delusional misidentification syndromes", a group of conditions comprehending Capgras delusion, intermetamorphosis, syndrome of the subjective doubles, autoscopic syndrome and reverse forms of subjective doubles and of the Fregoli syndrome itself: an individual, most often unknown to the patient, is now someone he knows "in disguise", and the individual is thought to be pursuing or persecuting him in some way (Oxford encyclopaedia). Otherwise, this syndrome is also considered as the illusion of a negative double, or a positive misidentification consisting of a belief that a persecutor has assumed the guise of various people whom the subject encounters in his daily life (Oxford dictionary). Oyebode adds another characteristic form of delusional misidentification syndrome, the delusion of inanimate doubles[1] (the belief that objects have been replaced by replicas). Finally,

some authors also consider a further form of delusional misidentification syndrome, "delusional misidentification of the mirror image", involving the delusion that the patient's mirror image is a separate individual[2]. The first description of this kind was made by Courbon and Fail[3], honouring a famous Italian actor and mimic (Leopoldo Fregoli, also known as "the quick change"): a 27-year-old woman, a waitress keen on theatre, started to think, and soon convincing herself, that two actresses, Robine and Sarah Bernhardt, dressed up to persecute her and often took on the guise of other people as neighbours or passers to torment her. In the original article, they report that "she is victim of enemies, of whom the main culprits are the actresses Robine and Sarah Bernhardt, whom she often went to see in the theatre. For years they have pursued her closely, taking the form of people she knows or meets, taking over her thoughts, preventing her from doing this or that, then forcing her to do things, stroking her and forcing her to masturbate" (p. 134). Someone also refers to the American actor Lon Chaney, "the man of a thousand faces", but the eponym is universally accepted as Fregoli. Christodoulou[4] stated how an imaginary persecutor is considered under the form of many different people, otherwise familiar. Anyway it needs no similarity at the basis of misidentification, in fact the "substitution" is thought to be "psychic", not "physical". Of course, this does not means that the case discussed by Courbon and Fail was really the first: clinically speaking, and psychopathologically, for example, there is the description operated by French psychiatrist François Leuret (1797-1851) in his main opera[5].

Materials and methods

It seems that has never been described a case of Fregoli syndrome due to cannabis abuse.

I myself was able to personally observe and treat a case induced by the use of cannabis: unfortunately, however, the patient did not give me consent to publish his story, so I cannot produce a real case report. I can argue that I saw a case for the first time, but that this person did not agree to provide consent, so I can only mention its existence without being able to describe it in detail.

Very summarily he drank about seven/eight cups of coffee a day; he smoked cigarettes from the age of about eighteen: he stopped often but for short periods, usually spontaneously, yet on one occasion he stopped smoking for about ten consecutive years (at the time he smoked a habitual quantity varying between ten and fifteen cigarettes/day); he habitually consumed very low alcohol, except in no-alcohol drinks, but in the past he had observed, and for a long time, periods of obvious abuse, even problematic; he did not remember particular problems with driving or with the Law, but he certainly had had episodes of drunkenness, even reckless, and had participated, or had been involved, in fights; he smoked cannabinoids for at least five consecutive years, continuously and excessively, when he had reached the point of constantly smoking fifteen joints a day; he never used any other substance of abuse; he had no behaviors suggestive of further addiction phenomena and declared that he was passionate about poker but has never felt a problematic attraction towards it; he states that he has always had normal results in laboratory tests commonly and periodically performed; recalled a negative neuroradiological exam a few months before; blood pressure has always been good, more recently it has seen some modest increases but that have not determined chronicity in this sense, falling well within the limits of the norm even currently; recalled never having had reports of electrocardiographic anomalies, not even when he observed the sports suitability tests.

At a certain point in the psychiatric examination he created a new connection, among similar others: even "looking out from the balcony, doctor, think about it, I saw people walking down the street, and I didn't recognize them; or rather, I didn't know them but I felt like I did; in fact, I was sure of it: those weren't just any passers-by, think about it, they were people I knew well, people I knew well, and I don't know why there was something wrong; as if they were strangers but instead they were my friends… sorry, maybe enemies, but I mean there was something familiar in their strangeness… uhm, you see, I can't explain, it was all so strange, in short those passers-by had to do with me, and even if they didn't seem like anyone in particular they were people I knew well". When asked if he had ever had similar experiences, he simply answered no, with a suggestive sense of wonder, typical of someone who believes that the other has understood exactly how that experience, and only that one, belongs to his distorted thinking. He was then also asked if he had ever had, so to speak, opposite experiences, that is, suspecting that behind his acquaintances there were strangers, lookalikes or people who had replaced their relatives by imposture: but he did not seem in the least interested in this possibility, with the typical dismay of someone who thinks he is not crazy.

Certainly a clinical diagnosis of Fregoli syndrome was made: the patient accepted an antipsychotic treatment, with Olanzapine, achieving complete symptomatic remission; at the same time he stopped using cannabis. Then he was well for a long time, until he resumed the use of cannabis and developed the same disease again (Fregoli syndrome). He was treated again with the same therapy and also stopped using cannabis again. Subsequently he suspended the pharmacological therapy too and was definitively well. However a simple report of cannabis-induced Fregoli syndrome, after a complete literature review, could draw attention to this rare, but

possible, phenomenon.
This clinical history, together with this type of evolution, suggests that the Fregoli syndrome was due to a chronic intoxication by cannabis and not to schizophrenia or other psychotic disorder, neither it seems to have been a spontaneous ill.
Finally this work could constitute, on the one hand, an interesting review, complete and detailed, on the psychiatric and neurological nature of the syndrome, insinuating, on the other hand, among researchers who are interested in addictions, the doubt that even a substance of abuse can induce this syndrome.

Results

It seems that has never been described a case of Fregoli syndrome due to cannabis abuse, in fact.
A simple report of cannabis-induced Fregoli syndrome, after a complete literature review, could draw attention to this rare, but possible, phenomenon.
The Fregoli syndrome can be due to a chronic intoxication by cannabis and not only to schizophrenia or other psychotic disorder, neither it must be always a spontaneous ill.
The psychiatric and neurological nature of the syndrome are not the only causes able to produce the peculiar symptomatology: the present work insinuates, among researchers who are interested in addictions, the doubt that even a substance of abuse can induce this syndrome.

Discussion

Fregoli syndrome and schizophrenia/psychosis

Few studies have examined samples of people with cannabis-induced psychotic symptoms[6]: schizophrenia spectrum disorders were diagnosed in 44.5% of the sample illustrated in that quoted study, new psychotic episodes of any type in 77.2% (cit.). There is also a considerable debate regarding the causal relationship between cannabis abuse and psychiatric disorders[7]. Ksir and Hart[8] wrote, instead, that exists a plethora of scientific articles addressing the relationship between cannabis use and psychosis, however wishing future research studies focusing exclusively on the cannabis-psychosis association. On the other hand, although rarely, Fregoli syndrome has been described in literature as a neuropsychiatric illness: as a manifestation of schizophrenia, naturally[9,10]; as co-occurrence with inter-metamorphosis, in schizophrenia[11]. Originally, McEvedy et al.[12] described a case with twice manifestations during "manic" aspects of a schizophrenic: with regard to a man and concerning a dog. Turkiewicz et al. described the case of a 62-years-old woman with coexistence of Capgras and Fregoli syndromes in a paranoid schizophrenia presenting structural magnetic resonance imaging of periventricular and subcortical white matter hyperintensities on flair images mainly concentrated in the right frontotemporal region and bilateral frontotemporal volume loss[13].

Fregoli syndrome and neurodevelopmentale disorders

Moschopoulos et al. described an atypical association with Cotard's syndrome[14]; Silva and Leong described a case of an association between Capgras and Fregoli syndromes[15], but the same association has also been reported by Abreu et al.[16]; Brüggemann et al.[17] described a case with coincidence of erotomania and Fregoli syndrome with some interesting symptom constellations only rarely mentioned in the literature (one case was reported by Wright et al. in 1993[18]); to be honest, the link between erotomania and Fregoli-like syndromes started to be hypothesized by early 90's of last century: Collacot and Napier[19] described a case in a subject with Down's syndrome; moreover, we know that even the exemplary case included masturbation; Mann and Foreman[20] in a young male with learning difficulties (homo-erotomania); the one by Wright et al. (cit.) was a simple association. The syndromic association Capgras/Fregoli was reported by Ulzen and James[21] as example of co-occurrence of aggression and mental retardation (two cases). Finally it has been proven that neurodevelopmental factors may intersect with psychosis and delusional misidentifications[22]. According to Ribolsi et al., a central question is whether children with Autism Spectrum Disorders are able to distinguish between their subjective perceptions and reality: if the autistic condition implied an intrinsic difficulty in distinguishing between fantasy and reality, the recognition of a delusion in these patients would become very hard[23]. The presence of delusional beliefs includes, in fact, "unusual idea" (cit.).

Fregoli syndrome proper and in comorbidity

Brüggemann and Garlip, later[24], also discussed the case of a 24-year-old woman with the "special" coincidence: this letter (to the Editor) was so very interesting because of their preoccupation about drug screening, that was negative at all. Although more simply, Sanati and Mojtabai[25] resolved the case of a 51-year-old woman with a jealous theme. Teo et al.[26] presented a case in which "folie à deux" and Fregoli syndrome co-occurred ('secondary'); Silva and Leong furthermore described[27] an unusual presentation in which a patient believed that copies of his own mind inhabited the bodies of others: they named "subjective" this variant; they already referred to it as a "syndrome of the self"[28]; Mullholand and O'Hara[29], too, studied a 44-year-old man who presented an "unusual" form of Fregoli syndrome: he thought

he was incorporated into the same body with a female friend of him, so the Authors talked about "delusional hermaphroditism"; prior to '90s, however, Atwal and Khan already described a "very unusual" case[30]: the coexistence of three related syndromes to Capgras syndrome (namely the syndrome of Fregoli, the syndrome of intermetamorphosis and the syndrome of subjective doubles in the same patient during the course of his illness); these authors easily combine the organic hypothesis, suggesting the prescription of a CT scan of the head that resulted within normal limits: a 34-year-old male with paranoid disorder and borderline intellectual functioning, who presented with Capgras, Fregoli, intermetamorphosis and subjective doubles syndromes; he had also been diagnosed with paranoid schizophrenia but with chronic schizoaffective disorder too, for at least nine years; he had also manifested violent behavior and had been treated with antipsychotic drugs; the electroencephalogram showed generalized slowing probably secondary to medication, and the patient showed deficits on neuropsychological testing confounded by pre-existing mental retardation: the possible psychodynamic reading looked towards the search for symbolic representations of the patient's feelings, experiences and problems, alluding to the possibility of relating them to the feelings, hostile or not, reserved for the objects of his delusion. While only three cases of misidentification of sacred places were been reported previously in the literature, Awara et al.[31] reported the first case presenting a Delusional Misidentification Syndrome (DMS) – that they thought included a myriad of discrete but related syndromes, with Fregoli syndrome being one of the most common – emerging as a late onset first episode psychosis during the sacred journey o Hajj; starting from DMS, Papageorgiou et al.[32], already thought it was related to dissociation between recognition and identification process, and considered Working Memory (WM) responsible for the integration and manipulation of information: they studied a case of Capgras/Fregoli syndrome and found that DMS may be accompanied by WM dysfunction affecting some brain regions; they also found anomalies in the P300 component or P3 wave in Event-Related Potential (ERP). In 1988 de Pauw and Szulecka[33] reported four cases of violence associated with delusional misidentifications: one of them was a Fregoli syndrome; a similar article, during the same year, is available by Fishbain[34]. Ashraf et al.[35] associated Fregoli syndrome with verbal threats and aggressive behaviour, also reporting a case leading to an assault.

Fregoli syndrome in frankly neurological cases

Fregoli syndrome due to cerebral infarction is reported by de Pauw et al.[36]: this work appears to be important because of its mention, while describing a case report, about delusional misidentification in toxic-metabolic disorders; Duggal[37] – being interictal psychosis in patients with epilepsy highly correlated with temporal lobe epilepsy – noted however that there were only anecdotal reports on a similar aethiology of Fregoli syndrome, so he described a case (a 30-year-old woman) also discussing the neurobiological basis of the syndrome itself; a cerebrovascular accident was also involved in the case reported by Moriyama et al.[38], a 68-year-old woman with a 40-year history of schizophrenia: she developed Fregoli syndrome after a temporo-occipital damage; do Céu Ferreira et al.[39] described a 77-year-old woman who developed a Fregoli delusion with symptomatic exacerbation during the hemodialysis sessions (she had a chronic kidney disease receiving hemodialysis for 7 years, and she also had a vascular dementia). I, too, have been able to observe several cases of this syndrome (Fregoli) during neurocognitive disorders. Christodoulou hypothesized (cit.) that a strong organic component contributes to the pathogenesis of the Fregoli syndrome, after studying and describing seven patients; Joseph and O'Leary studied 10 patients with Fregoli syndrome comparing them to 10 matched controls: they found that Fregoli syndrome may be associated with anterior cortical atrophy[40]; Mojtabai presented a review of 34 cases of Fregoli syndrome in the English and French language literature: although an organic substrate was found in same cases, he suggested that it is the dominant psychotic theme which determines the content of the syndrome[41]; particular organic features have been reported by Feinberg et al.[42]: a 61-year-old man after a traumatic brain injury; and by Quadackers et al.[43]: Fregoli syndrome occurring in a 66-year-old female as result of a brain metastasis originating from a lung carcinoma; Hudson and Grace[44] investigated a patient who abruptly developed a disorder wherein she misidentified her husband as her deceased sister and claimed that her home was a duplicate of her real home that the Authors considered typical features of Fregoli syndrome and (respectively) Pick's reduplicative paramnesia (the belief that a person or place has been duplicated): they found, by magnetic resonance imaging, a discrete area of brain damage, probably ischaemic, in the anterior part of the right fusiform gyrus and anterior middle/inferior temporal gyri with parahippocampal and hippocampal atrophy (also interpretating clinically these data). They also claimed that a high order nervous system function that is devoted to the identification of faces is located in the adjacent midportion of the fusiform gyrus and a similar locus for environmental scenes, known as the parahippocampal place area, is present in the bordering parahippocampal gyrus. So delusional misidentification syndromes can be explained by disruption of the

connections of these highly specialised areas with the most anterior inferior and medial part of the right temporal lobe where, in fact, long term memory and mechanisms for the retrieval of information that are required for the visual recognition of faces and scenes, are stored (cit.). Stewart was able to associate it with Levo-DOPA treatment[45]. Paillère-Martinot et al.[46] studied thoroughly the case of a young woman by neuropsychological aspects, magnetic resonance imaging and PET scan, so discussed their findings. Salviati et al. published a case report of Fregoli syndrome in course of infection-related delirium[47]. de Bonis et al.[48] showed how a patient suffering from Fregoli syndrome had severe structural anomalies in the mapping of misidentified others and of the self. After all, Collins et al.[49] already noted how the Fregoli syndrome could have been considered an allied misidentification syndrome of Capgras syndrome, in a discussion about general consideration of its aethiology and comorbidity with organic disorders, also thinking that there are many other allied syndromes.

Fregoli syndrome in pregnancy, puerperium and breastfeeding

O'Sullivan and Dean described four cases occurring in the setting of puerperal psychosis, in relation to previously reported cases and finally proposed that the acute onset of the psychosis and ambivalence arising with childbirth were important factors in the pathogenesis[50]: in the same year de Pauw and Szuleka[51] replied to this paper through a letter to the Editor of the British Journal of Psychiatry, stating how the four case described did not correspond to the classic one of Courbon and Fail (the "first"); this observation is particularly important, still today, because it establish that there are many "false" cases in the literature, while the hallmark of the Fregoli syndrome is the delusional misidentification of familiar persons disguised as others.

Fregoli syndrome in other and various contests

Melca et al. reported how Fregoli syndrome was been rarely reported in patients with conditions other than schizophrenia-related disorders, diffuse brain disease and focal neurological illness[52]: so they thought that other associations could have been underreported, describing two original cases, both with severe and treatment resistant obsessive-compulsive disorder but one of them with paranoid personality disorder and the other one with a pervasive developmental disorder. Darby et al.[53] considered the brain connectivity of lesions causing delusional misidentifications, including the Fregoli syndrome: McKay and Furl replied with a scientific commentary but emphasized the validity of those finding for the "doxastic" aspect and mainly for the Capgras syndrome[54]. Brown et al. hypothesized a "familiar" form[55] of Fregoli syndrome. Margariti and Kontaxakis[56] wrote that co-occurrence of the different types of delusional misidentification syndromes, starting from Fregoli syndrome definition, must imply a common pathogenetic substrate ("disorder of the sense of uniqueness"). Strobbe-Barbat et al. said that have been reported a myriad of "inusual variants"[57]. At the same time there are undeniable differences: for example, there is an interpretative model, called "visuo-anatomical disconnection", proposed by Ellis and Young[58], which would explain Capgras syndrome but not that of Fregoli. Also Walther et al.[59] conclude to different pathophysiological mechanisms in the two disorders, and several authors agree on differentiate the two syndromes in two sub-groups[60]. Davies and Coltheart, illustrating their "two-factor theory of delusion", also considered Fregoli syndrome in depth: the first factor would explain why a delusional idea or hypothesis came to mind in the first place and the second factor would explain why the hypothesis was adopted and maintained as a belief rather than rejected, as it should have been, on the basis of the available evidence and the basic knowledge that contradicted it[61]: the characteristic of Fregoli syndrome was considered, here, a monothematic delusion. The presence of an autonomic response even to unknown faces was illustrated: in this case they adopted a suggestion by Ramachandran and Blakeslee[62], while noting that Langdon et al.[63] maintain, contrary to this hypothesis, that "Fregoli delusional content is generated when hyperarousal from the cognitive system to the PINs [person identity nodes] causes a known person to be identified as present, even in the absence of a corresponding face" (p. 628).

Fregoly syndrome and psychodynamic interpretation

Some psychoanalysts[64] believe that in Fregoli's syndrome the image of the body and the word corresponding to that image are separate: so others[65] argue that neither Fregoli syndrome nor other DMS are neurological disease, believing that although some studies enhance the existence of an organic neurological substrate, it should be underlined that there is no evidence for a tight relationship between specified brain lesions and DMS; the same authors, later[66], showed that the essential feature of Fregoli syndrome is the disjunction between "recognition" and "identification", and that these terms are far from being synonymous. There is a lot of evidence for psychodynamic interpretations, almost exclusively from the Freudian school. Capgras and Carrette[67], for example, were among the first to inaugurate this line of research thanks to an article in which they speculated on the role of the Oedipus complex. From a psychoanalytic point of view, more generally, the theory of Enoch et al.[68] hypothesizes that most people find things they like and things they don't like in loved ones: for some people these contradictory feelings can be-

come so tense that they create a sense of guilt that can be resolved through a splitting mechanism (a typical defense mechanism) that in turn generates a good person and a bad person: the "double", thus, can be "hated" without feeling any sense of guilt. The main flaw of this interpretation, however, is that there is no evidence other than the delusion itself; but this is not the only weak point: in fact, it would not provide any convincing explanation for cases that arose after organic brain injury, for example; finally, it fails to explain the "behavior" of the affected people. The "double" would necessarily be the object of negative emotions, in this way, while we know that some patients are neutral towards it and some may even end up being friendly and even attracted to it. Alexander, Stuss and Benson[69] reported a patient who described positive feelings towards "both wives", did not show anger or anguish for the abandonment of his first wife and, on the contrary, specifically expressed gratitude for having found a substitute: this, in fact, is a case of "severe head injury". In the study by Christodoulou himself[70], four of the eleven patients had a certainly propositive relationship with the person mistakenly identified, and he, who had subjected all eleven patients to a rich series of investigations, including "airencephalography", concludes by underlining the importance of the organic component of the syndrome despite only one of them having obtained a diagnosis of organic psychosis. Wallis[71], for his part, illustrated a review of cases where about 30% were friendly towards duplicates. The main problem of this research line, for the present study, is that it is based almost exclusively on Capgras syndrome, without ever mentioning even secondarily Fregoli syndrome. Many researchers, therefore, have preferred to concentrate on understanding the delusion itself, without presuming that it could be part of a more general syndrome: Signer[72], for example, organizes the substitution delusion in a "structure" that is part of another "structure", practically establishing a hierarchical nature, where the main problem includes the secondary problem that becomes part of the first – but especially Young – as schizophrenia could easily be considered from the perspective of "cognitive neuropsychiatry"[73] and from the psychological point of view[74]. The most solid theory still remains Freud's original one, although it has obviously never been addressed to a case of Fregoli syndrome: the ambivalence expressed by the dimension "I don't love him, I hate him" is a defensive modality expressed by the Ego, which rather than manifesting itself as the result of a split manifests itself as the product of denial and projection[75]; "I hate him because he persecutes me" provides the most powerful moral alibi for the sense of guilt so laboriously addressed by other subsequent researchers. The necessary distinction between the functional and the secondary genesis, even if organic, can help to understand the difference between primary Fregoli syndrome (or part of a broader syndromic morbid condition) and that induced by cannabis.

Fregoli syndrome in art and philosophy

Even philosophers have taken an interest in the question: for example, Giolito[75] has argued that in Fregoli syndrome, as in Capgras', emotional contents could influence the decision to consider an entity as a member of particular category. There also is a film by Charlie Kaufman, "Anomalisa", in which the protagonist suffers from this syndrome (2015).

Fregoli syndrome and substance use

Only Vecellio et al.[77] have reported a case (of two) in which a first single ecstasy dose produced an atypical paranoid psychosis with Fregoli syndrome and a series of complex-partial epileptic seizures with secondary generalization.

Cannabis use and psychosis

Cannabis-induced psychotic disorder is also a debated nosological construct[78]. Cannabis use is still considered an established risk factor for psychosis development[79]. No one reported a case of Fregoli syndrome, even in the case of Countries like Taiwan, where cannabis has become one of the most used illicit substances[80]. Marconi et al.[81] showed results of a meta-analysis enrolling a total of 66816 individuals: they observed a consistent increase in the risk of psychosis-related outcomes with higher levels of cannabis exposure in all included studies, so they confirmed a positive association between the extent of cannabis use and the risk for psychosis: not a case of Fregoli syndrome was reported. In an interesting and complete review Ortiz-Medina et al.[82] stated that cannabis use doubles the risk of developing psychosis in vulnerable people, even if the relationship between cannabis use and psychosis wasn't been fully elucidated: there wasn't a case of Fregoli syndrome in this review too. Pearson and Berry[83] argued that cannabis intoxication becomes cannabis-induced psychotic disorder once certain severity and duration criteria are met and cannabis-induced psychotic disorder is heavily associated with future schizophrenia diagnoses: but there wasn't a case of Fregoli syndrome. Finally, Hasan et al.[84] published a review of reviews, establishing that the scientific literature indicates that psychotic illness arises more frequently in cannabis users if compared to non-users, and that cannabis use is associated with a dose-dependent risk of developing psychotic illness; cannabis use was also associated with increasing of the relapse rate, hospitalization and positive symptoms: no mention about Fregoli syndrome. Cannabis can selectively increase extracellular dopamine concentrations in

the nucleus accumbens shell[85]; moreover, abstinence from chronic cannabinoid administration is associated with reduced dopaminergic transmission in the limbic system[86]: however, although the use of cannabis can be very dangerous in subjects who already suffer from psychiatric problems, in adolescents and in predisposed subjects, to the point of triggering "acute" psychotic episodes, there is no evidence that demonstrates with certainty how cannabis can, instead, "induce" a psychosis[87]. According to some researchers, the endocannabinoid system, which in normal conditions is involved in the restoration of homeostatic balance after neural stress, inflammation or cellular damage, appears deregulated in peripheral blood mononuclear cells of patients who have suffered a first episode of psychosis; the continuous use of cannabis could accentuate the malfunctioning of this endogenous protective system and some of the peripheral components of the endocannabinoid system could be used as biomarkers of the disorder: they, however, despite having considered a large amount of nervous and mental disorders in which this system, and in particular the CB_2 receptor, has been involved, have preferentially considered their results for the pharmacological modulation of the endocannabinoid system as a promising therapeutic target and not as a model to explain the onset of a psychosis starting from the chronic use of cannabis[88]. According to some authors, there would be no substantial difference between a primary psychotic episode and a psychotic episode induced by substances, going as far as to consider the insufficiency of any substance to cause a psychosis; it would be much more logical to conclude that the use of substances can favor the onset of a psychosis, without being able to induce it ex novo[89]. On the other hand, there are also studies that conclude in favor of the existence of a significant difference between primary psychoses and those induced by substances of abuse[90]. Maybe substance-induced and primary psychotic disorders as distinct entities[91]. Sometimes, of course, they show only little differences[92] or there are not many consistent differences[93]. The Author, in this paper, has the personal opinion that there are subtle but important differences between the two types of psychosis, yet he refers to the dictates of the DSM-5-TR™, considering the substance-induced psychotic disorder as a substance/medication-induced mental disorder, naturally distinguished from substance intoxication and substance withdrawal: it is potentially severe, usually temporary, but sometimes they are persisting central nervous system syndromes that develop in the context of the effects of substances of abuse, medications, and some toxin; all substance/medication-induced disorders share common characteristic: maybe, in this case, "with bizarre content"; in any case it may be identical in symptomatology to delusional disorder but can be distinguished by the chronological relationship of substance use to the onset and remission of the delusional belief; it is not better explained by another mental disorder or another medical condition but it is attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication)[94]. The case in question, though not fully reported for confidentiality reasons, points to an underexplored relationship between cannabis use and rare delusional misidentification syndromes. Therefore it should encourage further investigations or additional case reports since replicable evidence would be crucial to establishing a stronger causal link between chronic cannabis consumption and Fregoli syndrome. For the sake of completeness, it should be noted that some authors have presented a case of cannabis-induced delusion, but the formal diagnosis, according to the DSM-III-R criteria in force at the time of their observation (1993), was of "delusional disorder", in the context of which Fregoli's delusion had developed[95].

Conclusions

In summary, only two articles considered the possibility of an exotoxic etiology in Fregoli syndrome – however excluding it – and only one case report has general characteristics that are comparable to those that will be presented in the current paper, even if it refers to ecstasy and not to cannabis; cannabis use was correlated, finally, to a case of "delusional disorder" with Fregoli-like suggestive connotations. I finally invite interested scientists to search for other possible cases caused by cannabis.

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Conflict of interest statement

The author declares no conflict of interest.

The analysis was not pre-registered and the results should be considered exploratory.

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