The Neuropsychiatric Features of Fregoli Syndrome: An Individual Patient Meta-Analysis

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Abstract

Objectives: Fregoli syndrome is a rare delusion characterised by the belief that a familiar person is presenting themselves to the affected person disguised as others. Theories of delusional misidentification have suggested secondary ('organic') underlying mechanisms; however, the pathoaetiology of Fregoli syndrome has not been systematically evaluated. We sought to compare the neuropsychiatric features of Fregoli syndrome in primary and secondary psychosis.

Methods: A systematic review and patient-level meta-analysis were conducted. Five databases were searched. Demographic, diagnosis, delusional content, neuropsychiatric features, investigations, and treatment information was extracted. Random-effects models were calculated, and odds ratios (OR) and 95% confidence intervals (CI) estimated.

Results: 119 patients with Fregoli syndrome were identified: 62 (52%) with primary psychosis, 50 (42%) with secondary psychosis and 7 (6%) with an unclear aetiology. Patients with secondary psychosis were less likely to experience persecutory features than primary psychosis patients (OR = 0.26, 95% CI [0.10, 0.67], p = .0057). Moreover, secondary psychosis patients were more likely to experience Fregoli syndrome during a first episode of psychosis (OR = 11.00, 95% CI [2.45, 49.39], p = .0017). Right-sided brain lesions were more prominent than left-sided brain lesions in the total sample (χ^2 = 5.0, *p* = .025) and in the secondary psychosis subgroup (χ^2 = 4.26, *p* = .039).

Conclusions: This is the first meta-analysis investigating Fregoli syndrome. An estimated 42% of reported cases have a secondary aetiology. Findings enlighten our understanding of the symptomatology of Fregoli syndrome and have potential to be applied in future research and clinical practice.

Introduction

Fregoli syndrome is a delusion of misidentification first described by Courbon and Fail in 1927 [1]. It is characterised by the belief that a familiar person or people are presenting themselves to the affected individual disguised as others, meaning the appearance of individuals in the patient's environment is accurately perceived but they are serially misidentified as being a familiar individual [2]. Commonly, a patient with Fregoli syndrome misidentifies several individuals as being the same person, who are often perceived to be intentionally following the affected individual [3].

Over the past 80 years, delusional misidentification syndromes like Fregoli have posed challenges to mental health professionals due to a limited understanding of the aetiology [4], lack of effective treatment [5] and concerns around risk [6]. Earlier debates about misidentification delusions centred around whether they were best understood as 'organic' or secondary syndromes rather than 'functional' ('non-organic') or primary disorders [7,8]. More recently, however, case finding studies have noted that this simplistic classification does not account for the potential interactions between aetiology and presentation [9–11]. Indeed, there is emerging evidence of differences in the clinical presentation of misidentification delusions in the context of primary 'functional' and secondary 'organic' psychosis. For example, in a recent systematic review of Capgras syndrome, a related delusional misidentification syndrome where affected individuals misidentify familiar people as impostors, cases secondary to neurological disorder showed lower rates of paranoid delusions and higher rates of cognitive impairment in memory and visuospatial domains [12].

Despite Fregoli syndrome being phenomenologically distinct from other misidentification delusions [13] and likely arising from a characteristic aetiology [2], a comprehensive systematic review of the primary literature has never been performed. Using a patient-level meta-analytic approach, we sought to compare the neuropsychiatric features of patients with Fregoli syndrome arising as within primary or a secondary to neurological disorder.

Methods

A systematic review of all published cases of Fregoli syndrome was performed followed by a patient level meta-analysis comparing cases arising due to a primary or secondary psychosis. The study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14,15] (see Table 1 in supplementary materials). Furthermore, the meta-analysis was registered on the Open Science Framework.

Search strategy and selection criteria

Five electronic databases were searched (Pubmed, Medline, Embase, APA PsycINFO and Global Health) up to the 10th November 2020 using the following search terms with no date limits: "Fregoli delusion" OR "Fregoli syndrome" OR "delusions of misidentification" OR "delusional misidentification" OR "misidentification". After removal of duplicates, articles were screened by title and abstract, before the full paper was reviewed to confirm eligibility. Relevant systematic reviews and references of included cases were hand-searched for additional cases. The study search was conducted independently by two reviewers (MTD and AKD) and any disagreements were resolved by a third independent reviewer (GB).

Inclusion criteria required reports to be written in English and to include one or more patients with Fregoli reported at a case level. In instances where one or more publications reported data on the same patient, the most detailed study was used. To determine whether patients met clinical criterion, we assessed the reported delusional content against an adapted version of the criteria for identifying Capgras cases described by Bell and colleagues [9] (see Table 2 in the supplementary material). Only cases where diagnostic certainty was 'strong' or 'possible' were included in the meta-analysis.

Data collection and synthesis

An electronic data extraction tool was developed and piloted. Data extraction from all eligible publications was performed by a researcher (MTD). In addition, data from 20% of studies were extracted by a second researcher (AKD) independently and in parallel and a third researcher (G.B) arbitrated over any discrepancies (G.B). Data was extracted on i) demographics, ii) diagnosis, iii) delusional content, iv) other psychiatric features, v) investigations, and vi) treatment. Risk of bias was assessed using a modified version of the

Newcastle Ottawa Scale for case reports [16,17] (see Table 3 in the supplementary material). Using a 6-point scale, cases were rated as low risk of bias (scores of 5-6), medium risk of bias (scores of 2-4) or high risk of bias (scores of 0-1).

Statistical Analysis

First, summary statistics were computed for the whole sample. Thereafter, a patient level meta-analysis was performed comparing patients with a primary and a secondary psychiatric disorder. Cases where the aetiology was ambivalent/unknown or where insufficient data was reported (i.e., less than two main outcomes reported) were excluded from the meta-analyses. The primary analyses explored the neuropsychiatric features, neuroimaging and neurophysiological abnormalities and response to treatment. Secondary analyses were conducted on the content of the Fregoli delusion and neuroanatomical location of brain abnormalities.

A Wilcoxon rank sum test compared age differences and Pearson's chi-square test compared sex differences between the groups. Frequencies and percentages were computed and the differences between primary and secondary psychoses groups were assessed with odds ratios (OR) and 95% confidence intervals (CI) which were estimated using random-effects models. Post-hoc chi-square tests were conducted to compare the frequencies in right- and left-side lesions in the total sample and in the secondary psychosis subgroup. To assess the robustness of the results, sensitivity analyses explored the impact of risk of bias and diagnosis certainty. Cases at high risk of bias and cases assessed as 'possible' Fregoli syndrome according to the adapted diagnosis certainty scale were excluded, respectively. All variables were dichotomous, except age. The p-value was set a priori as 0.05. To adjust for multiple comparisons in the secondary analyses, p-values were adjusted using Bonferroni corrections (Jafari & Ansari-Pour, 2019). Statistical analyses were conducted in R version 4.0.4 [18], with the use of the psych [19], meta [20] and dplyr [21] packages. The datasets and full analysis available through Framework website code are the Open Science (https://osf.io/qygbm/?view only=731a081c5c5c4786b55a96de78f9d7c6).

Results

A total of 4,656 studies were identified from the study search and 154 full-text articles were screened (see PRISMA flowchart in Figure 1 of the supplementary material). The study search yielded 83 studies, which reported 119 cases of Fregoli syndrome patients.

Patient data was extracted from case reports (N = 61; 51%), case series (N = 37; 31%), experimental studies (N = 12, 10%) and abstracts (N = 9, 8%). Overall, 62 patients (52%) had Fregoli in the context of primary psychoses and 50 patients (42%) in the context of secondary psychoses. The remaining cases (N = 7, 6%) reported a mixed or unknown cause of psychosis and were thus excluded from the meta-analysis.

Cases which provided insufficient data (N = 23, 19%; references in supplementary materials) were also excluded from the meta-analysis, thus, a total of 89 Fregoli syndrome patients were entered into the meta-analysis: 55 patients (62%) with a primary psychiatric disorder and 34 patients (38%) with a secondary cause (Table 7 in the supplementary material for case descriptions). Of the patients included in the meta-analysis, 79 (89%) were rated 'strong' in terms of diagnostic certainty.

Diagnoses of included patients are detailed in Table 1. The majority of patients with a primary psychiatric disorder had schizophrenia (N =32, 58%). In contrast, patients with a secondary disorder were more evenly distributed across diagnoses with stroke (N = 9, 27%) and traumatic brain injury (N = 7; 21%) being the most common. Most patients with Fregoli in the context of a secondary cause had a neurological disorder (N = 26, 76%).

[INSERT TABLE 1 ABOUT HERE]

Risk of bias assessment

The majority of cases were rated as being at medium risk of bias (N = 46, 52%), followed by high risk of bias (N = 31, 35%) and low risk of bias (N = 12, 13%). Individual scores are reported in Table 7 of supplementary material.

Age and sex differences

Patients in the secondary psychosis group were significantly older (median 60 years, interquartile range (IQR) = 39 years) than patients in the primary psychosis group (median 33 years, IQR = 17 years) when tested with a Wilcoxon sign rank test (W = 510, p = .002). There was no significant difference in the proportion of females in the primary and secondary psychosis groups (49% and 50%, respectively; X^2 = 4.24 x 10⁻³¹, p = .99).

Neuropsychiatric features

Meta-analysis revealed patients with a secondary aetiology were significantly more likely to experience Fregoli as part of a first episode of psychosis (OR = 11.00, 95% CI [2.45, 49.39], z = 3.13, p = .0017). In contrast, they were less likely to experience persecutory delusions (OR = 0.26, 95% CI [0.10, 0.67], z = -2.76, p = .0057). All other neuropsychiatric features showed no differences between groups (Figure 1; table 4 in supplementary materials).

Primary psychosis (N=55)	Ν	%	Secondary psychosis (N=34)	Ν	%
Schizophrenia	32	58%	Stroke	9	27%
Bipolar disorder	7	13%	Traumatic Brain Injury	7	21%
Psychotic depression	5	9%	Neurodegenerative disease	5	15%
Schizoaffective disorder	4	7%	Substance-related	4	12%
Obsessive compulsive disorder	1	2%	Systemic illness	4	12%
Other causes ^a	6	11%	Epilepsy	3	9%
			Other causes	2	6%

 Table 1. Diagnoses in cases of Fregoli syndrome. ^aAdditional detail described in Table 5 of the supplementary material.

Neuroimaging abnormalities

In total, 21 (38%) patients with a primary psychotic disorder and 23 (68%) patients with a secondary cause reported neuroimaging results, detected by either CT (computed

tomography) and/or MRI (magnetic resonance imaging) scans. Of these patients, 4 (19%) and 19 (83%) patients in the primary and secondary psychosis groups, respectively, reported neuroimaging abnormalities (Table 2). This difference was statistically significant (OR = 20.19, 95% CI [4.36, 93.47], z = 3.84, p = .0001). We explored the neuroanatomical location of brain abnormalities detected. Almost three quarters of secondary psychosis patients had right hemispheric lesions (N = 14, 74%). In addition, over half had a frontal lobe abnormality (N = 10, 53%). In contrast, the majority of patients in the primary psychosis group showed bilateral lesions (N = 3, 75%). Random-effects models revealed no significant associations between psychosis aetiology and MRI abnormality location (Table 2). In a direct comparison of rightvs left-sided lesion frequencies, right sided lesions were more common across the whole sample (χ^2 = 5.0, p = .025) and this remained the case in the secondary psychosis sub-sample (χ^2 = 4.26, p = .039). Right-sided lesions were more common than left-sided lesions in the primary psychosis group, although the low total count (1 right-sided lesion, 0 left-sided lesions) excluded statistical analysis.

Lesion Location	Total (N = 23)		Primary Psychosis (N = 4)		Secondary (N =	p-value ª	
	n	%	n	%	n	%	
Right Side	15	65%	1	25%	14	74%	.65
Bilateral	9	39%	3	75%	6	32%	.95
Left Side	5	21%	0	0%	5	26%	.99
Frontal Lobe	12	52%	2	50%	10	53%	.99
Temporal Lobe	5	21%	3	75%	2	11%	.13
Temporoparietal	4	17%	0	0%	4	21%	.99
Frontoparietal	3	13%	0	0%	3	16%	.99

Table 2. Neuroimaging abnormalities in patients with Fregoli syndrome. ^a*p*-values adjusted using Bonferroni correction. Unadjusted p-values reported in Table 5 of supplementary material

A meta-analysis in patients who reported neuroimaging results between primary (n = 4) and secondary (n = 19) psychosis groups revealed no significant differences in neuropsychiatric features (see Figure 2 in supplementary data).

Delusional content

The majority of the patients with a primary (34/54, 63%) and secondary (18/30, 60%) disorder experienced more than one Fregoli delusion (i.e. identified more than one identity appearing in the guise of others). The content of the Fregoli delusions reported is detailed in Table 3. Patients with a secondary psychosis were more likely to mistakenly identify family members than patients with a primary psychosis (OR = 4.98, 95% CI [1.96, 12.65], z = 3.37, p = .007). Between groups, there were no significant differences in the categories of people from the environment that were being misidentified.

	Total ^c (N = 86)		Primary Psychosis (N = 52)		Secondary Psychosis (N = 34)		p-value ^d
	n	%	п	%	n	%	
Person in the environment							
Hospital staff and police	43	50%	23	44%	20	59%	.99
Stranger	25	29%	19	37%	6	18%	.64
Family member	19	22%	11	21%	8	24%	.99
Acquaintance ^a	10	12%	8	15%	2	6%	.99
TV character	3	3%	2	4%	1	3%	.99
Identity perceived							
Family member	36	42%	14	27%	22	65%	.007
Acquaintance ^a	25	29%	17	33%	8	24%	.99
Romantic interest ^b	13	15%	10	19%	3	9%	.99
Famous person	8	9%	7	13%	1	3%	.99
Person related to trauma	4	5%	3	6%	1	3%	.99

Table 3. Delusional content report in Fregoli syndrome patients with primary and secondary psychosis. ^a Acquaintances include neighbours, friends, school- and work-related people; ^b people with a romantic link also includes ex-partners; ^c Total number of cases that reported delusional content; ^d P-values adjusted using Bonferroni correction. Unadjusted p-values reported in Table 6 of supplementary material

Sensitivity analyses

Sensitivity analyses excluding cases at high risk of bias revealed no change in significant findings in the primary outcomes. However, the association between a secondary cause of psychosis and misidentification of family members became non-significant in the secondary

analysis (OR = 3.15, 95% CI [1.03, 9.61], z = -0.34, p = .44). Sensitivity analyses excluding cases rated as *possibly* Fregoli did not lead to any changes in the significant findings.

Discussion

The present study explored the difference in neuropsychiatric features associated with patients experiencing Fregoli syndrome associated with a primary or secondary ('organic') psychotic disorder. A total of 119 reported cases of Fregoli syndrome were found in the English literature since the first published description in 1927 [1], which averages 1.3 published cases per year. Of the reported patients, 42% (N = 50) experienced Fregoli in the context of a secondary cause, most commonly a neurological disorder.

This is the first comprehensive meta-analysis specifically exploring Fregoli syndrome. However, previous research has explored the neuropsychiatric features of delusions of misidentification more broadly. An earlier review of 260 case reports of delusions of misidentification explored the most frequent associated neuropsychiatric features, which included paranoid symptoms, depression, auditory hallucinations and aggressive behaviour [22]. In a more recent systematic review of Capgras syndrome, the most common type of misidentification delusion, a significant difference in the neuropsychiatric features, was observed between patients with a primary and a secondary aetiology [12]. Specifically, patients with a secondary aetiology were more likely to experience visual hallucinations, to exhibit neuroimaging and neurophysiological abnormalities and to have memory and visuospatial impairments [12]. Moreover, they were less likely to have formal thought disorder, to experience auditory hallucinations, to suffer from other misidentification and paranoid delusions, and to show violent behaviour.

In patients who underwent neuroimaging, it was notable that right-sided lesions were particularly common. In addition, there was an over-representation of patients with lesions in the frontal lobe. The preponderance of right and frontal neuroanatomical lesions in patients with misidentification delusions has been reported in previous studies [23,24]. Darby and Prasad (2016) investigated a sample of 61 patients with various delusions of misidentification and found that 63% had right frontal lesions and that the frequency was significantly higher than that of lesions in other lobes, or in the left hemisphere [25]. Furthermore, a recent MRI study exploring brain connectivity of lesions related with delusions of misidentifications found that almost all the patients in their sample (n = 17) had lesions in brain areas functionally connected to the right frontal cortex [26] and that this was specific

misidentification delusions, compared to other neurological syndromes. This highlights the critical importance of the right frontal regions that were found in our sample of Fregoli syndrome patients. Dysfunction of the right hemisphere and frontal lobe are associated with the misplacement of familiarity, as well as faults in reality monitoring and memory integration [27]. It is plausible that these cognitive impairments may result in incoherent and false explanations, inducing Fregoli syndrome and other delusions of misidentification.

Persecutory features associated with Fregoli syndrome were more likely to occur in primary psychosis patients than in secondary psychosis patients. Interestingly, this association has also been reported in Capgras syndrome by Pandis and colleagues (2019). This finding may be explained by the high proportion of patients in the primary psychosis groups with schizophrenia for which paranoid delusions are one of the most common symptoms [28]. Additionally, results showed that patients with a secondary cause of psychosis were older, also consistent with the findings in Capgras syndrome [12] and with several organic causes of delusions of misidentification being age-related, such as stroke and neurodegenerative disorders [29].

One of the key findings from this meta-analysis was that almost half of all patients with Fregoli syndrome had a secondary cause. This suggests that clinicians should have a high index of suspicion of an organic aetiology for any patient presenting with Fregoli syndrome and therefore request relevant neuroimaging investigations, such as magnetic resonance imaging (MRI). Clinicians should be particularly mindful of older patients and patients presenting with Fregoli in the context of a first psychotic episode where neurological causality is likely to be more prevalent. However, we sound a note of caution. Reviews of Capgras delusion based on case reports and series have reported high levels of organic aetiology [12] and forensic risk [30] which have not been found in subsequent case finding studies [9,10] potentially suggesting that certain features may be over-represented in the published literature. Fregoli delusion may be a phenomenological marker for secondary aetiology, however future case findings studies remain key to answering this question.

Strengths and limitations

There are several strengths to the current meta-analysis. The study comprises the largest synthesis of cases of Fregoli syndrome and therefore provides the most comprehensive and up to date review of literature. Furthermore, a case-level approach yielded a highly granular level of detail, including exploration of descriptive psychopathology. In addition, we were able to evaluate the diagnostic certainty of cases based on reported phenomenology, providing a high degree of confidence regarding caseness. Furthermore, sensitivity analyses indicated that the results were robust to risk of bias and diagnosis certainty.

There are, however, certain limitations. Most cases were extracted from case reports and case series which generally constitute low levels of evidence. Indeed, most cases were at medium or high risk of bias. Further, the inherent nature of case reports and case series meant that these publications were likely to be over enriched for unusual or extreme presentations. This could have led to an overestimation of patients with a secondary cause of psychosis. Furthermore, there was a lack of consistency in the reporting of clinical features across studies, which led to several missing data points, lowering the statistical power and increasing the risk of a type one error. In particular, the number of patients with a primary cause of psychosis who reported neuroimaging results was very low. These issues may have introduced publication bias as well as outcome reporting bias and therefore caution is called for in generalising our results.

Future directions

Case finding studies will be required to determinate the prevalence of primary and secondary causes of Fregoli syndrome. This information, combined with sensitivity and specificity, would allow positive and negative predictive values to be estimated for phenomenology as a potential guide to secondary causation. However, due to the rarity of Fregoli, recruitment is likely to present a substantial challenge to such an endeavour. The use of electronic health records may be a fruitful alternative [9]. In addition, structural and functional neuroimaging studies are necessary to further the investigations regarding the lateralisation of abnormalities to advance our understanding of the neural correlates of Fregoli syndrome.

Conclusion

Fregoli syndrome is a rare delusion of misidentification commonly associated with secondary 'organic' causes in the published literature. We found patients with a secondary cause were more likely to be older, present as part of a first episode of psychosis and to have neuroimaging abnormalities than patients with a primary 'non-organic' cause. Findings are informative to our understanding of potential mechanisms underlying Fregoli syndrome. Furthermore, results suggest clinicians should have a high index of suspicion for a secondary cause when a patient presents with Fregoli syndrome, with MRI indicated in all cases.

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