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Network analysis of psychotic manifestations among cocaine users

1) Introduction

Psychotic experiences can be described along a continuum ranging from no psychotic experience at all, to clinical psychosis (Hélène Verdoux & van Os, 2002). In such a description, psychotic symptoms can be experienced in the general population. Considering sub-threshold expressions of psychotic experiences, they are transitory in 80% of non-clinical individuals (van Os and Reininghaus, 2016). A cross-national study conducted on 31,261 adult responders worldwide showed that 5.8% of the general population had already experimented a psychotic symptom (McGrath et al., 2015). At the end of the continuum, lifetime prevalence of psychotic disorders is estimated to be 3.5%, of which schizophrenia diagnosis represents a third (Os et al., 2017).

One of the most commonly used tool to assess psychosis as a continuum is the Peters Delusion Inventory (PDI). It explores psychosis proneness with 21 items using the introductory expression “do you ever feel as if”, such as « do you ever feel as if things in magazines or on TV were written especially for you? ». On average, individuals endorse 6.7 ± 4.4 of the proposed psychotic experiences. On the other hand deluded individuals (patients receiving neuroleptic medication) had a significantly higher average score of 11.9 ± 6.0 (Peters et al., 2004). This questionnaire could also differentiate students from schizophrenic patients in another study (3.27 ± 3.71 vs 5.32 ± 5.31 , $p < 0.0001$) (Wang et al., 2017)(Wang et al., 2017a).

Exploring the risk factors modulating the expression of psychosis-like signs in non-clinical populations may better contribute to elucidate the etiology of psychosis than research restricted to subjects at the endpoint of the distribution of the psychotic dimension (Verdoux et al., 2001). Among the most studied risk factors, cannabis use frequency, but not alcohol use frequency has been the focus of several investigations (Verdoux et al., 2003).

Cocaine-induced psychotic symptoms could also be a good model. Indeed, transient Cocaine Induced Psychotic Symptoms (TCIPS), such as visual hallucinations and persecution delusions are frequent, with 48% to 86% of cocaine use disorder patients assessed in care describing at least one psychotic symptom induced by cocaine (Roncero et al., 2017a; Vorspan et al., 2012b). These symptoms are more frequent with crack (than cocaine) and there is converging evidence of a dose-effect relationship (Kalayasiri et al., 2006; Vorspan et al., 2011). A systematic review of psychosis associated with stimulant use found that a single dose of a stimulant drug can produce a brief increase in

psychosis ratings in 50-70% of participants with schizophrenia and pre-existing psychotic symptoms (Curran et al., 2004). More specifically, among patients diagnosed with a cocaine use disorder, those with an independent psychotic disorder were more likely to have disorganized speech and grossly disorganized or catatonic behavior (Vergara-Moragues et al., 2016b), while patients with TCIPS only, described more frequently grandiosity delusions, and less frequently visual hallucinations.

Thus, our aim was to use a network analysis to get a better knowledge on the architecture of previously described risk factors and how they contributed to two different measures of psychosis (psychosis proneness and transient cocaine induced psychotic symptoms) in the quasi-experimental model provided by cocaine users.

2) Methodology :

Subjects:

This study is a secondary analysis conducted on 180 patients from a multicentric, descriptive study about transient cocaine induced psychotic symptoms. **Patients were cocaine users recruited in addiction care centers in Paris and Paris suburb.** This study had been approved by the relevant ethic committee (CPP Ile de France IV) in March 2011 (NCT01569347) and all patients gave informed written consent before participating to the assessment.

Assessment:

Substance use disorders were evaluated with the DSM (Diagnostical and Statistical Manual) IV criteria (American Psychiatric Association, 2004). Psychosis proneness was assessed using the PDI (Peters et al., 2004), leading to a total score ranging from 0 to 21. We also rated TCIPS using the SAPS-CIP questionnaire (Scale for the Assessment of Psychotic Symptoms- Cocaine Induced Psychosis) (Cubells et al., 2005), a clinician-rated interview leading to a total score from 0 to 15. This scale is divided into three subscales assessing hallucinations, delusions and cocaine-related behavior, each scored from 0 to 5. Schizophrenia diagnosis was collected from medical records. Furthermore, we collected patients' socio-demographic and clinical data.

Statistical analysis:

Data are described using means (SD) and frequencies (percentages), and we performed Anova's and Pearson's correlation tests.

A Network analysis is a system of relationships among several variables (symptoms), where each symptom is represented by a node and the relationship between symptoms are represented by

edges. An edge represents pairwise relations between two variables when all other variables are controlled for (Borsboom and Cramer, 2013).

Relevant variables selected to be significantly associated with SAPS-CIP total score or PDI at the previous step were included in the network. Because this study is exploratory, the statistical threshold retained was $p < .05$. The analyses were done using JASP 0.8.6.0 software.

3) Results

Population characteristics :

Among the 180 patients, there were 76% male; the mean age at the time of the interview was 38 (± 8) years old. The mean age of onset of cocaine use was 24 ± 7 years old, a large majority of the sample preferentially used cocaine (72% vs crack) and most patients snorted it (65% vs 35% injected or inhaled it). Eighty eight percent of the sample met the DSM IV criteria for cocaine dependence and 65% used it daily. Patients were poly substances dependent with 86% fulfilling the criteria for lifetime tobacco dependence, 58% for alcohol, 47% for opiate dependence, 56% for cannabis dependence and 39% for benzodiazepine dependence.

The mean total PDI score was 7.2 ± 4.3 with a minimum of 0 and a maximum of 18. Seventeen patients suffered from schizophrenia (8.8%) according to the medical records. The mean total SAPS-CIP score was 7.1 ± 3.4 , the hallucination score (HAL) was 1.7 ± 1.6 , the delusion score (DEL) was 2.4 ± 1.4 and the cocaine-related behaviour score (CRB) was 3.0 ± 1.1 . In this study, almost all our subjects (91%) described at least one psychotic symptom induced by cocaine at any moment of their lifetime cocaine use history (HAL or DEL or CRB ≥ 2).

Univariate analysis

Comparison of the SAPS-CIP different scores (total, delusions, hallucinations and cocaine-related behavior) with PDI score showed statistically significant positive correlations (Table 1), meaning that TCIPS are higher among patients with high psychosis proneness. There was no association between SAPS-CIP scores and schizophrenia diagnosis but schizophrenia diagnosis was associated with higher PDI score ($p=0.004$). Patients with schizophrenia had higher PDI scores (10.2 ± 4.0) than patients with no schizophrenia (6.9 ± 4.2).

Regarding the other substances, there was no association between the PDI score and cocaine or opiate dependence, but benzodiazepine ($p=0.037$), cannabis ($p=0.007$) and alcohol ($p=0.034$) dependences were associated with higher PDI scores (Table 2).

The SAPS-CIP total score was associated with cocaine dependence ($p < 0.001$) but with no other substance dependence. Furthermore, this score was higher regarding daily cocaine use rather than less frequent use ($p < 0.001$). Lastly, schizophrenia diagnosis wasn't significantly associated to any substance dependence (benzodiazepine, cocaine, alcohol or opiate) other than cannabis ($p = 0.01$) (see Table 3). The PDI score was significantly higher in the case of: schizophrenia diagnosis ($p = 0.004$), rapid routes of cocaine administration ($p = 0.04$), and crack use ($p = 0.014$).

Network:

All significant variables ($N = 8$) associated with the PDI or SAPS-CIP total scores were entered in the model: lifetime cocaine dependence, cocaine frequency of use, cocaine route of administration, cocaine preferential product, lifetime cannabis dependence and schizophrenia. The total PDI and SAPS-CIP score were also entered in the model. The total sparsity was 0.071.

The centrality measures (see fig 1) showed that the product preferentially used (cocaine vs crack) was a core node in this model, which was related to other cocaine use variables, but also to transient cocaine induced psychotic symptoms, psychosis proneness and, to a lesser extent, schizophrenia.

Cocaine variables/markers of heavy cocaine use (preferential product, way of administration, frequency use and cocaine use disorder) were strongly associated, forming one cluster. Cocaine use disorder's strongest association was with the frequency of use, meaning a strong relationship between cocaine use disorder and daily cocaine use. The SAPS-CIP total score was associated with cocaine variables on the one hand and the PDI score on the other hand. ***In this conception, transient cocaine induced psychotic symptoms is a mediator between intensive cocaine use and psychosis proneness.***

The Network analysis also highlighted a relatively independent cluster where cannabis use disorder was associated to schizophrenia and schizophrenia was associated to psychosis proneness. In this cluster, ***schizophrenia is a mediator between cannabis use disorder and psychosis proneness.***

4) Discussion

This study is, to our knowledge, the only one using network analysis to study risk factors of psychotic symptoms among cocaine users.

First, the bivariate analysis showed that risk factors associated with higher SAPS-CIP scores and PDI scores were not exactly the same, even though TCIPS and psychosis proneness were correlated.

The results of that first step are in line with the literature on several points. The high TCIPS prevalence found in our study (91%) is close to what was observed in several studies including previous independent samples assessed by our team (Roncero et al., 2011, 2017a; Roncero et al., 2014; Roncero et al., 2013, 2014; Trape et al., 2014; Vergara-Moragues et al., 2014; Vorspan et al., 2012b).

The prevalence of Schizophrenia diagnosis was quite small in our study recruiting patients in an addiction care setting (9%), which is comparable to other studies among SUD patients ~~has also been found in other epidemiological studies~~ (Libuy et al., 2018; Roncero et al., 2016). But, contrarily to previous studies on TCIPS (Roncero et al., 2017b; Trape et al., 2014; Vergara-Moragues et al., 2014; Willi et al., 2016), we choose not to exclude subjects with a preexistent psychotic disorder to be able to embrace the whole psychosis continuum. Our results are also consistent with the literature in identifying risk factors of high SAPS-CIP score, thus representing different ways to assess a higher severity of cocaine exposure. Especially, this was the case for lifetime cocaine dependence and daily use, that were previously associated with a higher risk of TCIPS (Kalayasiri et al., 2010; Smith et al., 2009; Trape et al., 2014; Vergara-Moragues et al., 2014; Vorspan et al., 2012a). Conversely, we lacked to find an association between cocaine routes of administration and TCIPS, unlike previous studies (Roncero, et al., 2013; Vorspan et al., 2012a). This could be explained by the covariation of other severity markers with the route of administration for cocaine use (Gossop et al., 1994).

Second, the network analysis enabled us to study altogether three dimensions of psychosis (psychosis proneness, schizophrenia and TCIPS). It showed that pervasive psychosis proneness is a mediator between transient cocaine-induced psychotic symptoms (and intensive cocaine use) on the one hand, and schizophrenia (and heavy cannabis use) on the other hand. Cannabis use disorder was here only weakly associated with psychosis proneness and TCIPS.

This result contrasts with previous findings, suggesting that cannabis dependence could be a major predictive factor of psychotic symptoms among cocaine users (Libuy et al., 2018; C. Roncero et al., 2011).

We want to emphasize that lifetime cannabis use disorder was observed in our sample to be associated with a higher PDI-21 score. Thus, we can hypothesize that the association between early heavy cannabis use and TCIPS observed in previous studies (Kalayasiri et al., 2010) was mediated by psychosis proneness, that none of those studies measured, especially because early cannabis use can durably influence brain maturation, probably in interaction with genetic factors (French et al., 2015).

This is in line with several studies conducted in the general population, bringing a lot of evidence of an association between heavy cannabis use and psychotic symptoms. Verdoux et al. found that a high frequency of cannabis use was independently associated with positive and negative psychotic experiences (Verdoux et al., 2002). A meta-analyze found an link between cannabis and incidence and prevalence of psychotic symptoms (Linscott and van Os, 2013). It has been described that psychotic-

like symptoms in non-clinical population are a risk of developing a psychotic disorder that could lead to seeking health care (Hanssen et al., 2005; Kelleher and Cannon, 2011; Poulton et al., 2000)

In clinical populations, based on prospective cohort studies, there was an association between cannabis use and an increased risk of characterized psychotic disorder (Henquet, 2005; Moore et al., 2007). It was also described that patients with schizophrenia had higher PDI-21 scores.

Finally, the network analysis refines the previous knowledge by adding this mediating role of psychosis proneness between cannabis use and cocaine-induced psychosis and solves the discrepancies between these pieces of literature.

The sample size, the use of two validated questionnaires, and the choice not to withdraw patient with a schizophrenia diagnosis and the network analyze without a-priori are strengths of our study. Our results illustrate the possibility to map multidimensional experiences in a network to better understand how the variables interact (Wigman et al., 2017).

Among the limits, the multiple substances dependences, could have contributed to transient induced psychotic symptoms (Vergara-Moragues et al., 2016). Similarly, because of the retrospective design of the study, it wasn't possible to record patient's treatment history or cocaine dosage, which could represent confusion factors. The retrospective design could result in memorization bias that could involve difficulties to determine the cause-effect relationship between cocaine use and TCIPS (Vergara-Moragues et al., 2014). Furthermore, one could object that we based the difference between primary psychotic disorder and TCIPS on the clinician judgement.

The comparability of the results to other studies is limited because several other tools exist to measure TCIPS, such as the CEQ (Roncero et al., 2014), and more than 40 tools (Lee et al., 2016) to measure psychosis proneness.

Finally, the network analyze of transversal data should be interpreted carefully because it does not reveal the causal association in between symptoms. Also, this analyze conceptualizes the interaction of variables (symptoms) among the whole sample and does not take into account intra-individual variability.

Several other studies assessing the same samples with both TCIPS and psychosis proneness, especially with a prospective design including periods of heavy *versus* lower cocaine use could help to better describe the mutual links between those two psychotic phenomena.

Conclusion

Using a network analysis, we could observe a differential risk factor architecture in psychosis phenomena in patients with cocaine use disorder. On one hand, intensive cocaine use was associated with transient cocaine-induced psychotic symptoms (TCIPS). Those TCIPS correlated with psychosis proneness. On another hand, pervasive psychosis proneness was associated with schizophrenia and heavy cannabis use. In such, we refine the previous knowledge on heavy cannabis use being a risk factor for TCIPS. We showed that the link is not direct but mediated by psychosis proneness.

Declaration of interests: none

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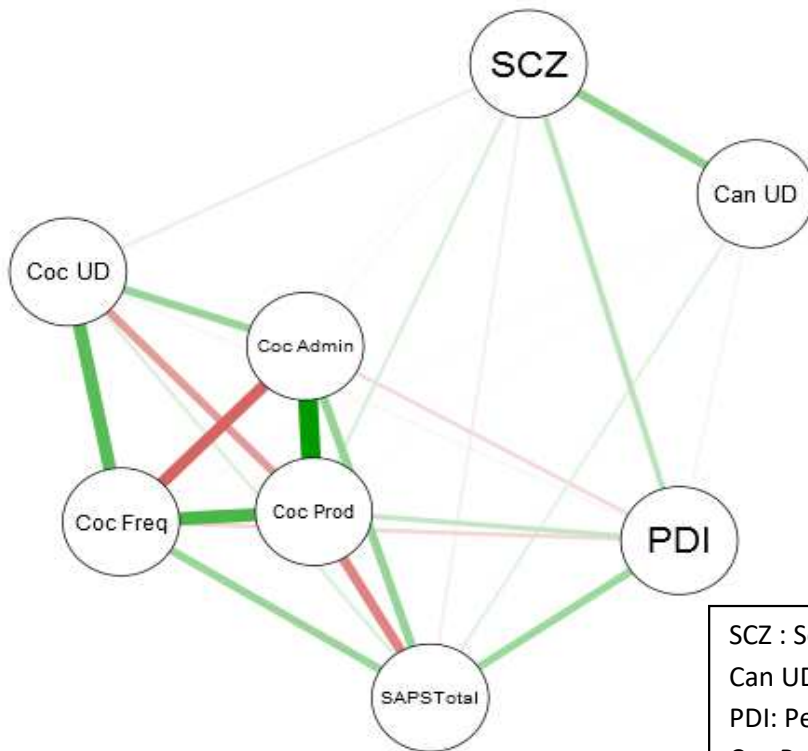
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Figure 1: Network analysis (representation and centrality measures)



SCZ : Schizophrenia diagnose
 Can UD : Cannabis Use Disorder
 PDI: Peters Delusion Inventory
 Coc Prod: cocaine product
 Coc Admin: cocaine way of administration (sniffed or other way)
 Coc Freq: cocaine frequency (daily or less often)
 Coc UD: cocaine use disorder
 SAPS-CIP : Scale for the Assessment of Psychotic Symptoms – Cocaine Induced Psychosis

Centrality measures per variable

Variable	Network		
	Betweenness	Closeness	Strength
Can UD	-0.957	-1.798	-1.486
Coc Admin	-0.957	0.512	0.907
Coc Freq	0.064	0.443	0.878
Coc Prod	1.085	1.084	1.334
Coc UD	-0.957	-0.349	-0.165
PDI	-0.447	0.176	-0.685
SAPSTotal	0.574	0.960	0.162
SCZ	1.595	-1.029	-0.945

Table 1: Associations between SAPS-CIP and PDI scores

	SAPS-CIP hallucinations	SAPS-CIP Delusions	SAPS-CIP Behavior	SAPS total score
Pearson Correlations with PDI score	0.35	0.22	0.07	0.29
P value	<0.001	0.002	0.337	<0.001

SAPS-CIP : Scale for the Assessment of Psychotic Symptoms – Cocaine Induced Psychosis,

PDI : Peters Delusion Inventory

Table 2: Significant associations between PDI scores and dependences (ANOVA's tests)

ANOVA	Average PDI score	Standard Deviation PDI	P value
No Benzodiazepines Dependence	6.7	4.1	p=0.037
Benzodiazepines Dependence	8.1	4.3	
No Cannabis Dependence	6.1	4.3	P=0.007
Cannabis dependence	7.9	4.3	
No alcohol dependence	6.39	4.2	P=0.034
Alcohol dependence	7.78	4.38	

PDI : Peters Delusion Inventory

Table 3: associations of clinical variables with the SAPS-CIP and PDI questionnaire

SAPS-CIP total score		N	Mean	Standard Deviation	ANOVA F / Spearman ρ	p-value
Lifetime cocaine dependence	Yes	156	7.52	3.218	19.340	<.001*
	No	22	4.27	3.411		
Schizophrenia	Yes	16	7.62	3.096	.382	.537
	No	156	7.07	3.448		
Cocaine Administration	Smoked or injected	63	7.40	3.206	.653	.420
	Sniffed	115	6.97	3.514		
Preferential product	Crack+/- cocaine	44	6.80	3.268	.523	.471
	Cocaine	134	7.22	3.455		
Frequency	Daily	115	7.79	3.186	15.179	<.001*
	Less often	61	5.77	3.437		
Lifetime cannabis dependence	Yes	99	7.47	3.363	3.580	.060
	No	71	6.48	3.414		
PDI-21 total score		N	Mean	Standard Deviation	ANOVA F / Spearman ρ	p-value
Lifetime cocaine dependence	Yes	158	7.25	4.328	.186	.667
	No	22	6.82	4.697		
Lifetime cannabis dependence	Yes	100	7.95	4.356	7.565	.007*
	No	72	6.10	4.361		
Schizophrenia	Yes	16	10.12	4.020	8.621	.004*
	No	158	6.91	4.275		
Cocaine Administration	Smoked or injected	64	8.09	4.381	4.296	.040*
	Sniffed	116	6.70	4.292		
Preferential product	Crack+/- cocaine	45	8.58	4.213	6.206	.014*
	Cocaine	135	6.73	4.330		
Frequency	Daily	117	7.44	4.298	.923	.338
	Less often	61	6.77	4.551		

SAPS-CIP : Scale for the Assessment of Psychotic Symptoms – Cocaine Induced Psychosis,

PDI : Peters Delusion Inventory