Progress in Neuropsychopharmacology & Biological Psychiatry 109 (2021) 110250

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Prevalence of antipsychotic-induced extrapyramidal symptoms and their association with neurocognition and social cognition in outpatients with schizophrenia in the "real-life"

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ARTICLE INFO

Keywords:
Extrapyramidal symptoms
Schizophrenia
Neurocognition
Social cognition
Antipsychotics

ABSTRACT

First generation antipsychotics (FGAs) are more likely to induce extrapyramidal side-effects (EPS) than second generation antipsychotics (SGAs), and EPS have been shown associated to cognitive deficits in schizophrenia. So far, no study has explored the relationships between EPS and social cognition (SC) in people with schizophrenia. Therefore, we assessed the prevalence of EPS in a large sample of drug-treated community-dwelling persons with schizophrenia and explored their relationships with patients' neurocognitive and SC abilities.

875 patients underwent EPS, psychopathological, neurocognitive and SC assessments by means of standardized measures. Relationships between EPS, psychopathology and neurocognitive and SC measures were investigated by correlation tests. Moreover, a partial correlation network was computed by means of a network analysis.

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https://doi.org/10.1016/j.pnpbp.2021.110250
Received 21 October 2020; Received in revised form 10 January 2021; Accepted 13 January 2021
Available online 20 January 2021

256 patients were treated with FGAs alone or in combination with SGA and 619 with SGAs. EPS were significantly more frequent in FGA-treated group than in the SGA-treated one. Patients with EPS disclosed a more severe psychopathology and were more impaired in neurocognitive and SC measures compared to those without EPS. Disorganization, expressive deficit, and duration of illness were significantly associated to both neurocognitive and SC measures while EPS were associated to neurocognitive measures only. The network analysis showed that parkinsonism was the sole EPS directly connected to both psychopathological and neurocognitive indices whereas no direct connection emerged between EPS and SC measures.

Present findings confirm that EPS are still present in the era of SGAs and contribute, together with other clinical variables, to the neurocognitive but not to the SC impairment of patients with schizophrenia.

1. Introduction

Schizophrenia is a severe psychiatric disorder characterized by serious cognitive dysfunctions, which encompass a broad array of non-social and social cognitive domains such as attention, vigilance, working memory, visual and verbal learning, speed of processing, problem solving and social cognition (SC) (Nuechterlein et al., 2004; Kalkstein et al., 2010; Green et al., 2019). Importantly, neurocognitive deficits have been shown strongly associated with real-life functioning of people with schizophrenia (McClure et al., 2007; Bowie et al., 2008; Galderisi et al., 2014); so, research aimed to advance knowledge of variables that may impact on cognitive performances of people with schizophrenia is mandatory to provide more appropriate therapeutic interventions to improve their real-life functioning.

The pharmacological treatment of schizophrenia relies mostly on first generation (FGA) and second generation (SGA) antipsychotics. FGAs are associated to adverse side-effects, especially extrapyramidal side-effects (EPS) including subjective and objective akathisia, acute dystonia, parkinsonism and tardive dyskinesia, which occur in 50–75% of patients treated with these drugs (Keks, 1996; Casey, 1997). SGAs have been associated to a milder EPS profile and, therefore, greater tolerability than FGAs (Glazer, 2000; Caroff et al., 2002). EPS have been indicated as a potential factor contributing to cognitive deficits in schizophrenia. Indeed, EPS have been associated to poorer patients' attention, worse global cognitive performance, deficits in motor skills and verbal learning (Palmer et al., 1999; Tanaka et al., 2012; Cuesta et al., 2014; Fervaha et al., 2015). In the same line, deficits in spatial working memory, visuo-spatial abilities and attention have been associated with tardive dyskinesia in people with schizophrenia (Pantelis et al., 2001; Wu et al., 2013), although the CATIE study did not find any significant association between tardive dyskinesia and cognitive impairment, after controlling for some confounding variables (Miller et al., 2005).

To the best of our knowledge, so far no study has explored the relationships between EPS and SC in people with schizophrenia. SC refers to how people think about themselves and others in the social world and includes those cognitive domains that are employed in socially relevant situations, such as emotional processing, theory of mind, social perception, social knowledge and attribution style (Green et al., 2005; Penn et al., 2008). It is widely acknowledged that people with schizophrenia present serious and generalized deficits in SC (Chan et al., 2010; Fett et al., 2011; Savla et al., 2013) and SC impairment negatively affects patient's functioning in the real-life (Galderisi et al., 2014). Therefore, the assessment of the relationships between EPS and SC abilities in people with schizophrenia is worth to be explored.

In the present study we assessed the prevalence of EPS in a large and well-characterized sample of community-dwelling Italian persons with schizophrenia, recruited in the context of a multicentre study of the Italian Network for Research on Psychoses (NIRP), and explored their relationships with patients' neurocognitive and SC abilities. We hypothesized that EPS are more prevalent in patients treated with FGAs compared to those treated with SGAs and that patients with EPS perform worse than those without EPS on both neurocognitive and SC tasks.

2. Subjects and methods

Patients consecutively admitted to the outpatient units of 26 Italian university psychiatric clinics and/or mental health departments were screened for the study from March 2012 to September 2013. Inclusion criteria were: 1) diagnosis of schizophrenia according to DSM-IV criteria, confirmed with the Structured Clinical Interview for DSM-IV-Patient version (SCID-I-P); 2) age between 18 and 66 years; 3) no history of head trauma with loss of consciousness; 4) no history of moderate to severe mental retardation or of neurological diseases; 5) no alcohol and/or substance abuse in the last 6 months; 6) no current pregnancy or lactation for fertile women; 7) ability to provide an informed consent; 8) no treatment modifications and/or hospitalization due to symptom exacerbation in the last 3 months.

All subjects signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals.

The study was approved by the Ethics Committees of participating centers and has been conducted in accordance with the principles of the Declaration of Helsinki (59th World Medical Association General Assembly; October 2008).

2.1. Clinical assessment

2.1.1. Psychopathology

Positive and disorganization symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Scores for the dimensions "disorganization" and "positive symptoms" were calculated based on the consensus 5-factor solution proposed by Wallwork et al. (2012). Negative symptoms were assessed by means of the Brief Negative Symptom Scale (BNSS) (Strauss et al., 2012), an instrument that allows the identification of two separate factors: a) avolition, consisting of anhedonia, asociality and avolition, and b) expressive deficit, including blunted affect and alogia. The Italian version of the scale was validated as part of the Italian Network project (Mucci et al., 2015).

2.1.2. EPS

EPS were assessed by the St. Hans Rating Scale (SHRS) (Gerlach et al., 1993) which includes four subscales: akathisia, dystonia, parkinsonism and dyskinesia. Each subscale has one or more items, with a score ranging from 0 (absent) to 6 (severe).

2.1.3. Neurocognition

Neurocognitive assessment was performed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) that is considered the 'state-of-the-art' neuropsychological battery for research purposes in schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008). This battery allows the assessment of six distinct cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem solving. Co-norming and standardization of the Italian MCCB test scores was carried out as described by Kern et al. (Kern et al., 2008; Mucci et al., 2017). The test battery provides also a neurocognitive composite score, which represents a

comprehensive measure of all neurocognitive domains.

2.1.4. Social cognition

SC was assessed by: 1) the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) managing emotion section, which examines the regulation of emotions in oneself and in one's relationships with others; 2) the Facial Emotion Identification Test (FEIT) (Kerr and Neale, 1993), which examines emotion perception, and 3) the Awareness of Social Inference Test (TASIT) (McDonald et al., 2006), which is organized into 3 sections: emotion recognition; social inference (minimal) that permits the assessment of comprehension of sincere versus sarcastic exchanges; social inference (enriched) that is the assessment of comprehension of lies versus sarcasm. These instruments have been described in detail in Rocca et al. (2016). SC variables were standardized with respect to Italian normative data. The mean of standardized z-scores of MSCEIT, FEIT and TASIT was used as a SC composite score.

2.1.5. Chlorpromazine equivalent daily doses (CED) and Risperidone equivalent daily doses (RED) of antipsychotic drugs

CED of antipsychotic (AP) drugs were calculated as suggested by Gardner et al. (2010) while RED of AP drugs were calculated based on the daily defined doses method of Leucht et al. (2016), for 607 patients for whom the current daily AP dosages were available.

2.2. Statistics

Differences among groups on categorical variables (gender distribution and prevalence of EPS) were investigated by using Pearson's chi square test. Student's *t*-test and two-way analyses of variance (ANOVAs) were used to assess group differences on demographic and clinical variables with respect to gender and type of AP treatment. In case of statistically significant group differences on these indices, group comparisons were performed by entering them as covariates.

Multivariate analyses of variance (MANOVAs) were run to investigate differences in psychopathology, neurocognition and SC between patient groups with or without EPS. When a significant main effect was found in the MANOVA, an analysis of covariance (ANCOVA) with duration of illness and AP CED as covariate was run to investigate intergroup differences on psychopathology and cognitive measures.

The association of EPS and psychopathology with neurocognition and SC were investigated by means of Pearson's correlation test followed by stepwise multiple regression analysis in which the neurocognitive composite score and the SC composite score were entered as dependent variables, while independent variables were EPS, psychopathological domains, duration of illness and AP CED.

In order to disentangle the associations between EPS and both neurocognition and SC taking into account the weight of positive and negative symptoms, we computed a partial correlation network in which connections reflected correlations between pairs of nodes after adjusting for the influence of all other variables in the network (Epskamp and Fried, 2018). A 'least absolute shrinkage and selection operator' (LASSO) regularization was applied (Friedman et al., 2014); this procedure shrinks small partial correlations, setting them to zero, so only the most robust partial correlations remain visible (McNally, 2016). The Extended Bayesan Criterion (Chen and Chen, 2008), a parameter that sets the degree of regularization/penalty applied to sparse correlations, was set to 0.5 in this analysis. Network analysis was performed using R, version 3.4.4, qgraph package. Accuracy of edge-weights were assessed by nonparametric bootstrapping (nboots = 2500) using the bootnet package (Epskamp et al., 2018).

3. Results

Of the 921 patients participating in the multicenter study of the Italian Network for Research on Psychoses (Galderisi et al., 2014), 875 were included in this study, since they completed all the requested assessments. They were 607 men and 268 women; all were treated with AP drugs: 130 of them received FGAs (103 received a single FGA and 27 a combination of FGA), 619 received SGAs (539 received a single SGA and 80 received a combination of SGA) and 126 received a combination of a FGA plus a SGA. For the purposes of this study, the latter were included in the group treated with FGAs, which so was composed of 256 patients.

The prevalence of EPS in the whole sample and in patients subgrouped according to FGA or SGA treatment is shown in Table 1. Parkinsonism was the most frequent EPS in the whole sample as well as in each group of treatment, followed by akathisia, tardive dyskinesia and dystonia. As expected, all types of EPS were significantly more frequent in the FGA-treated group than in the SGA-treated one. No significant difference emerged in the distribution of male and female patients between patients with EPS and those without EPS in the whole group ($\chi^2 = 2.23$, $p = 0.1$), the FGA-treated group ($\chi^2 = 2.16$, $p = 0.1$) and the SGA-treated group ($\chi^2 = 0.02$, $p = 0.8$).

The prevalence of EPS according to the received AP medication is summarized in Supplementary Table 1. Briefly, in the group of patients treated with a single SGA, the highest frequency of any EPS occurred in those treated with quetiapine (42%), followed by clozapine (39%), risperidone (37%), paliperidone (36%), olanzapine (30%), aripiprazole (27%) and amisulpride (10%). Haloperidol was the most prescribed FGA either as the sole drug ($n = 78$) or in combination with another FGA ($n = 23$) or with an SGA ($n = 25$): in these groups the rates of EPS were 42%, 74% and 44%, respectively, with an overall prevalence rate of 48.4%. No significant correlation emerged between the AP CED and EPS St. Hans scale scores.

Compared to patients without EPS (EPS-), those with any EPS (EPS+) were significantly older, had an earlier age of illness onset, a longer illness duration and received higher CED or RED of AP (Table 2). Patients treated with FGA were older, had a longer disease duration and received higher CED or RED of AP than those treated with SGA in both EPS+ and EPS- group (Supplementary Table. 2). Because of these statistically significant differences, age, duration of illness and AP CED were used as covariates in the comparisons between EPS+ and EPS- groups. Since AP CED were available for 607 patients (238 EPS+ and 369 EPS-) the intergroup comparisons were run two times: the first one in the whole patient sample and the second one in the 607-patient subgroup.

The MANOVA on psychopathological measures comparing EPS+ and EPS- groups showed a significant overall group effect in both the whole sample (Pillai trace = 0.092, $F_{4,870} = 22.09$, $p < 0.00001$) and the subsample with AP CED (Pillai trace = 0.115, $F_{4,602} = 19.62$, $p < 0.00001$). When age, duration of illness and AP CED were introduced as covariates in the analysis where appropriate, ANCOVA disclosed significant intergroup differences in all the psychopathological domains, with EPS+ patients showing a more severe psychopathology than EPS- patients (Table 3).

The MANOVA on cognitive measures comparing EPS+ and EPS- patients showed a significant overall group effect in both the whole sample (Pillai trace = 0.089, $F_{11,728} = 6.48$, $p < 0.00001$) and the subsample with AP CED (Pillai trace = 0.104, $F_{11,525} = 5.59$, $p < 0.00001$). Since neurocognitive and SC measures were corrected for age, gender and education, age was not included as covariate in the subsequent ANCOVA. When duration of illness and AP CED were introduced as covariates in the analysis, where appropriate, ANCOVA disclosed significant intergroup differences in all the cognitive measures except for MSCEIT domain, with EPS+ patients showing significantly lower neurocognitive and SC scores than EPS- patients (Table 3).

When the neurocognitive and the SC composite scores were compared between EPS+ and EPS- patients, they resulted significantly lower in EPS+ patients in both the whole sample and the subsample with AP CED (Table 3).

Table 1
Prevalence of Extrapyramidal Side Effects (EPS) in the whole sample and according to antipsychotic treatment.

	Subjective akathisia	Objective akathisia	Any akathisia	Dystonia	Parkinsonism	Tardive dyskinesia	Any EPS
Whole sample ($n = 875$)	117 (13.3%)	135 (15.4%)	151 (17.6%)	16 (1.8%)	283 (32.4%)	52 (5.9%)	346 (39.5%)
Subjects treated with FGA ($n = 130$) or with FGA + SGA ($n = 126$)	50 (19.5%)	60 (23.4%)	64 (25.0%)	9 (3.5%)	116 (45.3%)	25 (9.7%)	132 (51.5%)
Subjects treated with SGA ($n = 619$)	67 (10.8%)	75 (12.1%)	87 (14.0%)	7 (1.1%)	167 (26.9%)	27 (4.3%)	214 (24.4%)
Chi-square test[a]	11.85	17.79	14.67	5.74	27.82	9.46	21.87
P value	<0.001	<0.001	<0.001	0.01	<0.001	0.002	<0.001

FGA = First Generation Antipsychotic; SGA = Second Generation Antipsychotic.
[a] Comparison between subjects treated with FGA or FGA + SGA and subjects treated with SGA.

Table 2
Demographic and clinical characteristics of patients with (EPS+) or without (EPS-) Extrapyramidal Symptoms.

	EPS + (n = 326)	EPS – (n = 529)	t	p
Age, yrs	42.37 ± 10.99	38.85 ± 10.4	4.79	<0.001
Age at onset, yrs	23.46 ± 7.59	24.45 ± 6.97	1.98	0.047
Duration of Illness, yrs	18.91 ± 10.9	14.39 ± 9.89	6.33	<0.001
Chlorpromazine Equivalent Daily Dose, mg	561.18 ± 372.41[a]	472.58 ± 296.61[b]	3.24	0.001
Risperidone Equivalent Daily Dose, mg	9.33 ± 6.23[a]	7.88 ± 4.44[b]	3.19	0.001

[a] $n = 238$.
[b] $n = 369$.

3.1. Correlation analyses

Statistically significant negative correlations were observed between both neurocognitive and SC composite scores and psychopathology or presence of any EPS, indicating that a worse psychopathology and the occurrence of EPS were associated to poorer neurocognitive and SC functions in both the whole patient sample and the subsample with AP CED (Supplementary Table 3). Moreover, duration of the illness was significantly and negatively correlated to SC composite score ($r = -0.28$, $p < 0.001$ in the whole sample; $r = -0.32$, $p < 0.001$ in the sub-sample with AP CED) but not to neurocognitive composite score ($r = -0.01$, $p = 0.6$ in the whole sample; $r = -0.07$, $p = 0.08$ in the sub-sample with AP CED).

The stepwise multiple regression analyses showed that the neurocognitive composite score was associated with PANSS disorganization score, BNSS expressive deficit score, presence of EPS and duration of illness and that, overall, these variables explained 12.6% of the variance of the neurocognitive score in the whole sample and 15.1% of its variance in the subsample with AP CED (Table 4). The SC composite score, instead, resulted associated with PANSS disorganization scores, BNSS expressive deficit scores and duration of illness and, overall, these variables explained 15.2% of the variance of the SC composite score in the whole sample and 20.6% of its variance in the subsample with AP CED (Table 4).

3.2. Network analysis

Partial correlation network is depicted in Fig. 1. The non-parametric bootstrap showed that 95% confidence intervals (CIs) of edge weights are quite tight (Supplementary Fig. 1) and allow to interpret the estimated edges. The network shows that parkinsonism was the sole EPS directly connected to both psychopathology and neurocognition. Indeed, parkinsonism was directly and negatively connected to the neurocognitive composite score ($\rho = -0.104$) and directly and positively connected to both PANSS positive symptoms ($\rho = 0.053$) and BNSS expressive deficit ($\rho = 0.099$). No direct connection emerged between SC composite score and any EPS.

4. Discussion

The first aim of our study was to measure the prevalence of EPS in AP-treated patients with schizophrenia in the real-life. We found prevalence rates of EPS of 51.5% in patients treated with FGAs and of 24.4% in patients treated with SGAs, that is the rate of EPS in patients treated

Table 3
Psychopathology and Cognitive Domains of patients with (EPS+) or without (EPS-) Extrapyramidal Symptoms in the whole sample and the sub-sample with Antipsychotic (AP) Chlorpromazine equivalent daily doses (CED).

	Whole Sample ($n = 875$)				Sub-sample with AP CED ($n = 607$)			
	EPS+ ($n = 346$)	EPS – ($n = 529$)	F	p	EPS+ ($n = 238$)	EPS – ($n = 369$)	F	p
PANSS Disorganization	3.1 ± 1.5	2.3 ± 1.4	36.18	$<1 \times 10^{-10}$	3.0 ± 1.4	2.2 ± 1.3	30.01	6×10^{-9}
PANSS Positive	11.0 ± 4.9	8.9 ± 4.3	28.57	15×10^{-9}	10.8 ± 4.7	8.5 ± 4.17	23.28	1×10^{-7}
BNSS poor Emotional Expression	15.3 ± 7.8	11.5 ± 7.8	40.37	$<11 \times 10^{-10}$	15.0 ± 7.3	11.1 ± 7.9	28.69	1×10^{-8}
BNSS Avolition	23.1 ± 9.1	19.3 ± 9.5	27.64	18×10^{-9}	23.2 ± 9.0	18.7 ± 9.6	25.44	6×10^{-8}
Speed Processing	28.3 ± 11.4	32.8 ± 11.1	33.35	1×10^{-9}	28.0 ± 11.6	33.3 ± 10.8	29.86	7×10^{-9}
Attention/Vigilance	35.0 ± 10.7	38.3 ± 11.4	16.36	0.00001	34.4 ± 10.9	39.7 ± 11.4	26.77	1×10^{-8}
Working memory	32.1 ± 12.4	36.5 ± 11.2	25.08	6×10^{-8}	31.9 ± 12.9	37.1 ± 11.0	21.78	3×10^{-7}
Verbal Learning	33.4 ± 12.4	36.1 ± 11.6	10.24	0.001	33.2 ± 12.8	36.8 ± 11.5	11.44	0.0007
Visual Learning	28.1 ± 13.6	34.9 ± 14.7	42.48	$<1 \times 10^{-10}$	27.9 ± 13.4	35.3 ± 14.4	32.23	2×10^{-9}
Problem Solving	35.9 ± 9.7	38.6 ± 10.1	19.13	1×10^{-6}	35.8 ± 10.1	38.5 ± 10.4	11.78	0.0006
Neurocognition Composite Score	24.9 ± 12.1	30.4 ± 12.0	41.32	$<1 \times 10^{-10}$	24.4 ± 12.5	31.2 ± 11.8	38.64	$<1 \times 10^{-10}$
MSCEIT score	90.3 ± 13.9	90.5 ± 14.6	0.1	0.74	90.2 ± 14.1	91.4 ± 14.2	0.38	0.54
TASIT-1	19.0 ± 5.0	20.5 ± 5.1	6.26	0.01	19.1 ± 5.1	21.0 ± 4.6	8.73	0.003
TASIT-2	34.4 ± 11.0	38.9 ± 11.2	20.23	7×10^{-7}	34.6 ± 11.6	40.2 ± 10.7	21.88	3×10^{-7}
TASIT-3	35.5 ± 11.9	39.2 ± 11.4	11.65	0.0006	35.6 ± 12.8	39.6 ± 11.3	7.39	0.006
FEIT	35.1 ± 8.7	38.0 ± 7.9	14.22	0.0001	35.1 ± 8.9	38.2 ± 8.0	8.53	0.003
SC Composite	−1.63 ± 1.0	−1.23 ± 1.0	13.38	0.0002	−1.62 ± 1.1	−1.12 ± 1.0	14.63	0.0001

Table 4
Stepwise multiple regression analyses in the whole patient sample and in the subsample with antipsychotic (AP) Chlorpromazine equivalent daily doses (CED).

	Whole Sample (n = 875)		Subsample with AP daily CED (n = 607)	
	F	R^2	F	R^2
Neurocognition Composite Score				
EPS	39.05	0.02[d]	40.81	0.038[d]
BNSS Poor Emotional Expression	48.91	0.035[d]	32.89	0.022[d]
BNSS Avolition				
PANSS Positive Symptoms				
PANSS Disorganization	63.48	0.071[d]	54.04	0.085[d]
Illness Duration	30.76	0.005[a]		
CED				
Social Cognition Composite Score				
EPS				
BNSS Emotional Expression	51.53	0.006[b]	51.99	0.014[c]
BNSS Avolition				
PANSS Positive Symptoms				
PANSS Disorganization	93.65	0.098[d]	94.67	0.136[d]
Illness Duration	73.88	0.048[d]	71.84	0.056[d]
CED				

[a] $P < 0.02$.
[b] $P < 0.01$.
[c] $P < 0.002$.
[d] $P < 0.001$.

with FGAs, alone or in combination with SGAs, was almost twice that of patients treated with SGAs. Parkinsonism was the most frequent EPS followed by akathisia, tardive dyskinesia and dystonia. These results are consistent with a large body of literature reporting a higher prevalence of EPS with FGAs than SGAs (Yang et al., 2007; Rummel-Kluge et al., 2012; Leucht et al., 2013; Solmi et al., 2017), although some studies comparing SGAs with FGAs other than haloperidol revealed a less robust difference in EPS propensity between the two classes of drugs. Indeed, in the CATIE study the incidence of EPS in patients treated with SGAs did not significantly differ from those treated with perphenazine over the 18-month follow-up although more patients discontinued perphenazine owing to EPS and patients with tardive dyskinesia were excluded a priori from the perphenazine group (Lieberman et al., 2005). Similarly, in the CUtLASS study no significant difference in the EPS incidence emerged over a 12-month follow-up between patients treated with SGAs and those treated with FGAs, where the most frequently used FGA was sulpiride (Jones et al., 2006). In the same line, the EUFEST study did not find any significant difference in the EPS incidence between first-episode patients treated with haloperidol in low-dose and those treated with an SGA at 1-year follow-up (Rybakowski et al., 2014). Moreover, Yang et al. (2007) found that FGAs were prescribed in higher than recommended doses with respect to SGAs and hypothesized that this could be responsible to some degree for the higher occurrence of EPS in patients treated with FGAs compared to those treated with SGAs. In our sample, actually, we found that CED of FGAs were higher than those of SGAs, but we believe that this difference did not contribute to the higher prevalence of EPS in FGA treated individuals because such a

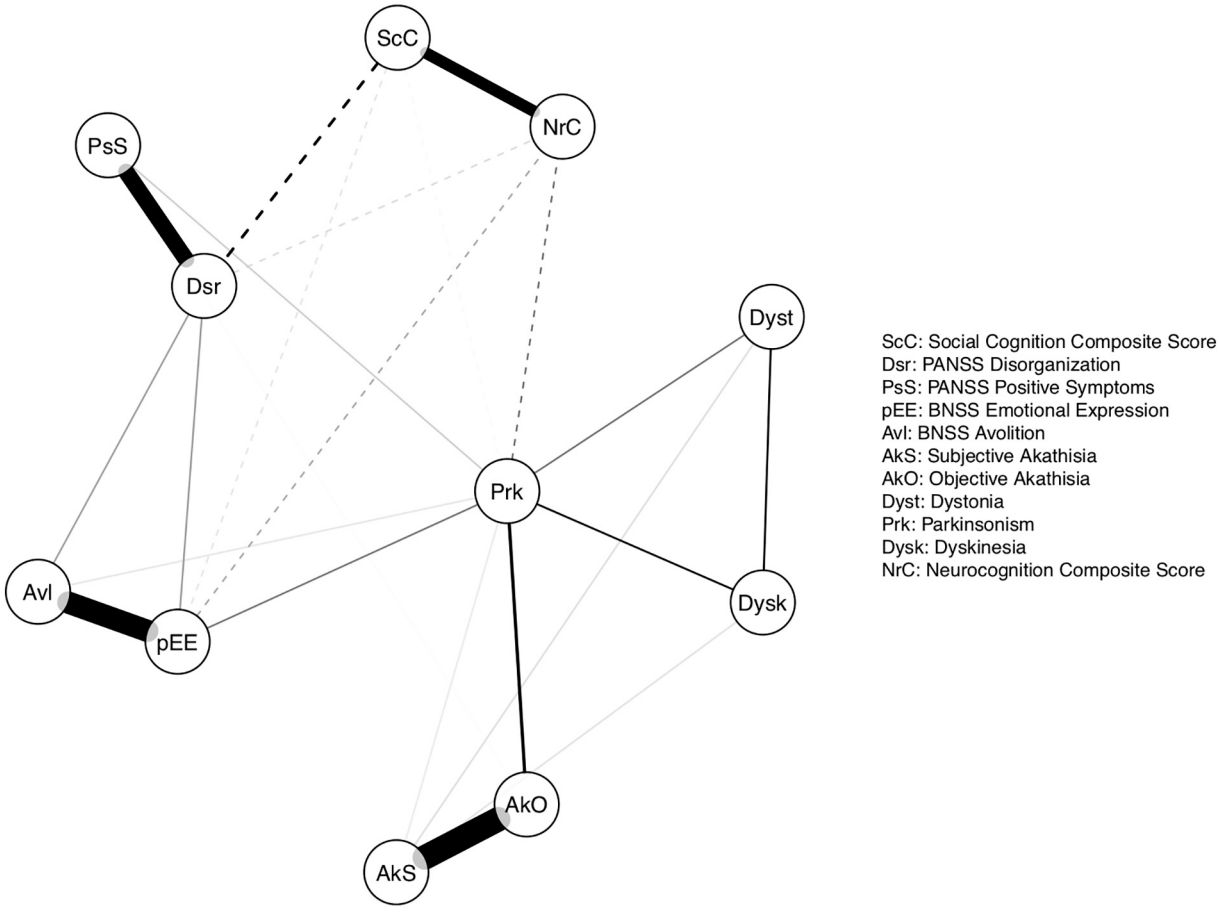

Fig. 1. Estimated partial correlation network among extrapyramidal symptoms, neurocognition and social cognition composite scores, positive and negative symptoms. The network is composed of nodes, representing the observed variables, and edges, representing the connections among them. Each connection in the network represents a partial correlation coefficient. The thickness of an edge graphically represents the magnitude of the association. Dashed connections represent negative coefficients.

difference occurred also in patients without EPS and no significant correlation was found between the AP CED and EPS St. Hans scale scores.

It is worth noting that most of the published studies assessing AP-induced EPS prevalence were based on prospective clinical trials comparing the efficacy/effectiveness of FGAs vs SGAs (Lieberman et al., 2005; Jones et al., 2006; Rybakowski et al., 2014) or were meta-analyses of published clinical studies (Rummel-Kluge et al., 2012; Leucht et al., 2013; Solmi et al., 2017) or were studies analyzing the co-prescribing rate of anti-Parkinson drugs as indicator of the presence of EPS using population databases (Yang et al., 2007). Here we provide a direct assessment of the prevalence of EPS in patients with schizophrenia treated with FGAs or SGAs in the real-life. To our knowledge only one study recently assessed the prevalence of AP-induced parkinsonism and tardive dyskinesia in a sample of stabilized community-dwelling outpatients with schizophrenia and found prevalence rates of 13.2% for parkinsonism and of 8.3% for tardive dyskinesia (Misdrahi et al., 2019). While the prevalence rate of tardive dyskinesia is in line with our data, that of parkinsonism is considerably lower with respect to the one we found. The relatively younger age and the shorter duration of the illness of the Misdrai et al.'s sample and the different scales used for the assessment of EPS may explain such a discrepancy. Anyway, these data taken together confirm that, in the real-life, the risk to develop EPS with SGAs is significantly reduced but it is not zero. In this line, it is quite surprising that among patients treated with SGAs we found the highest prevalence of EPS in those receiving quetiapine or clozapine. This is in contrast with literature data reporting both a lower occurrence of EPS with both SGA drugs (Arvanitis and Miller, 1997; Gerlach, 2002; Leucht et al., 2013; Solmi et al., 2017) and the lowest D2 receptor antagonist activity of quetiapine and clozapine as compared to other SGAs (Divac et al., 2014). A possible explanation of this discrepancy could rely on the use of the St. Hans scale to assess EPS. Indeed, this scale includes salivation and facial expression as symptoms contributing to the diagnosis of AP-induced parkinsonism and sialorrhea is a side effect of clozapine, while poor facial expression is also a negative psychopathological symptom. Therefore, it could be that in our clozapine-treated patients, an overestimation of parkinsonism would have occurred. Indeed, when we analyzed the diagnoses of parkinsonism based on the presence of salivation or reduced facial expression, we found that 8 patients were diagnosed with EPS based on the presence of salivation (7 individuals) or reduced facial expression (1 patients). By removing these patients, the percentage of clozapine-treated subjects with EPS decreased to 31%. This explanation did not apply to the group of quetiapine-treated subjects where only one subject had a diagnosis of parkinsonism based on poor facial expression. Alternatively, it could be that previous treatments with FGAs or SGAs could have induced EPS, which persisted when patients were switched to clozapine or quetiapine. This is especially plausible for clozapine, which is prescribed only in drug-resistant patients.

When we explored the association of EPS with psychopathology and cognitive functions, we found that, compared to patients without EPS, those with EPS presented more severe positive and negative symptoms and scored significantly lower on all the assessed neurocognitive domains and all but the MSCEIT scores of SC. These data are consistent with an extensive literature showing significant connections between poorer performance in neurocognitive and SC domains and more severe psychopathology in schizophrenia (Ventura et al., 2009; Rocca et al., 2016; Misdrahi et al., 2019).

Previous studies have assessed the association of EPS with neurocognitive functions in patients with schizophrenia and have consistently found that EPS were associated with worse neurocognitive performance, although some differences exist among the studies with respect to the compromised neurocognitive domains (Palmer et al., 1999; Krausz et al., 1999; Pantelis et al., 2001; Tanaka et al., 2012; Wu et al., 2013; Fervaha et al., 2015). To the best of our knowledge, so far, no study has assessed the relationships between EPS and SC in people with schizophrenia, although impairment in SC have been largely documented in this population (Chan et al., 2010; Fett et al., 2011; Savla et al., 2013). Here we report for the first time that EPS may contribute to SC impairment in people with schizophrenia, since patients with EPS performed worse than those without EPS on all the explored SC domains except for the regulation of emotions in oneself and in using emotions in interpersonal relationships, as assessed by the MSCEIT. Moreover, we found that PANSS disorganization scores, BNSS expressive deficit scores and duration of illness explained 11.1% and 15.2% of the variability of the neurocognitive composite score and the SC composite score, respectively. The presence of EPS, instead, was significantly associated to the neurocognitive composite score, contributing to explain a further 2% of its variability, but not to the SC composite score. This finding was confirmed by the network analysis, which showed that parkinsonism was the sole EPS directly connected to both psychopathology and neurocognition but not to SC. Therefore, it can be tentatively proposed that the impact of EPS on SC is not direct but mediated through the effects on neurocognition and/or psychopathology.

As for the mechanisms through which EPS may impair cognitive performance in schizophrenia, two main hypotheses have been put forward. The first one suggests that the worse cognitive performance of patients with EPS may be due to preexisting neural dysfunctions, which may imply also vulnerability to develop EPS following AP treatment (Waddington et al., 1993). The second hypothesis proposes that movement impairments affect the motor abilities required to perform certain neurocognitive tasks. In support of this hypothesis, impaired cognitive functions have been reported in patients with Parkinson's disease (Aarsland et al., 2003; Hely et al., 2008; Domellof et al., 2011) and cognitive impairment in drug-free schizophrenic patients with EPS with respect to those without EPS have been found to disappear after controlling for motor speed (Fervaha et al., 2015). However, while this hypothesis is intuitive in the association between EPS and cognitive tasks involving timed tests or motor movements, it is less likely when cognitive tasks do not involve movements (e.g. verbal learning, SC, spatial learning, letter-number span).

Some limitations of this study need to be discussed. First of all, we had no reliable information on the use of anticholinergic drugs to alleviate EPS symptoms in our patients. Anticholinergic drugs have been shown to impair cognitive functions, especially memory and attention, in patients with schizophrenia (Brébion et al., 2004; Minzenberg et al., 2004) and this could have affected our results. However, Potvin et al. (2015) did not find any significant effect of anticholinergics on the association between EPS and working memory deficits in a sample of patients with schizophrenia. A second limitation is represented by the lack of information regarding AP exposure antecedent to the present examination. Indeed, the duration of AP exposure has been reported significantly associated to the occurrence of EPS (Sampson et al., 2013).

In conclusion, the present study confirms that EPS are still present in the era of SGA and contribute, together with other clinical variables, to the neurocognitive impairment of patients with schizophrenia. Our network analysis demonstrates that parkinsonism is the EPS directly connected to neurocognitive performance of schizophrenic people and shows for the first time that EPS are not directly linked to the poor SC functioning of these patients, since their effects on SC are likely mediated through neurocognitive performance and/or psychopathology.

Ethical statement

This manuscript meets the guidelines for ethical conduct and report of research; it represents original material, has not been published previously, and is not being considered for publication elsewhere. Each author approved the final version of the manuscript and declared no biomedical financial interests or potential conflicts of interest.

Funding and disclosure

The study was partly funded by the Italian Society of Psychopathology and the Italian Society of Biological Psychiatry.

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The authors and the members of the Italian Network for Research on Psychoses declare that they have no competing financial interests in relation to the present work.

Declaration of competing interest

None.

Acknowledgement

None.

Author contributions

Drs Galderisi, Monteleone P and Maj had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Administrative, technical, or material support: Monteleone P, Cascino, Monteleone AM, Rocca, Rossi A, Bertolino, Aguglia, Amore, Collantoni, Corrivetti, Cuomo, Bellomo, D'Ambrosio, Dell'Osso, Frascarelli, Giordano, Giuliani, Marchesi, Montemagni, Oldani, Pinna, Pompili, Roncone, Rossi R, Siracusano, Vita, Zeppegno, Galderisi, Maj.

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The members of the Italian Network for Research on Psychoses contributed to the recruitment of patients; clinical, neuropsychological, and functional assessments and data quality control.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110250.

Appendix

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