Cognitive functioning in outpatients diagnosed with schizophrenia, with and without comorbid alcohol abuse

Funzionamento cognitivo in pazienti affetti da schizofrenia con e senza comorbidità per abuso alcolico

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Summary

Objectives

As the available studies suggest, inconsistently, that alcohol-abuse may be associated with greater cognitive impairment in schizophrenia patients, we compared cognitive functioning among matched schizophrenia patients with and without comorbid alcohol abuse, and matched healthy controls.

Methods

We applied the Milan Overall Dementia Assessment (MODA) cognitive test battery to compare cognitive functioning in patients with schizophrenia meeting DSM-IV criteria with (n = 17) or without (n = 40) lifetime alcohol abuse, verified with the Michigan Alcohol Screening Test (MAST), and patients versus healthy controls (n = 21) matched for age, sex, education and psychosis ratings.

Results

Cognitive performance was greatly impaired in both patient-groups compared to healthy controls, but only 6.2% more among patients with than without a history of alcohol-abuse. MODA and MAST scores were highly and inversely correlated.

Conclusions

Cognitive functioning in schizophrenia patients was substantially lower than in healthy subjects, as expected, but only slightly more impaired with a lifetime history of alcohol abuse.

Key words

Alcohol-abuse • Cognition • Comorbidity • MAST • MODA • Schizophrenia

Introduction

Estimated lifetime prevalence of substance-use disorders among schizophrenia patients is high (40-60%), especially among hospitalized patients, and most often involves alcohol-abuse [1 2], possibly in efforts at self-medication to ameliorate intolerable symptoms [3]. Cognitive impairments characteristic of schizophrenia include deficits in attention, memory, learning and executive functioning [4-6]. Cognitive deficits are also commonly found with alcohol abuse, including abnormalities in working memory, goal-selection, strategic planning and response-inhibition [7]. Cognitive deficits are not routinely assessed in schizophrenia patients, with or without comorbid alcohol abuse, even though they appear to have a strong relationship with poor clinical and functional outcomes [8 9].

Despite the common association of schizophrenia and alcohol abuse, it is not certain that the two conditions, combined, lead to worse cognitive impairments than either disorder alone. The available research findings remain inconsistent and inconclusive, with variable outcomes on tests of specific functions. Some findings include more severe impairments among dual-diagnosis patients on at least some cognitive tests [10 11], and with heavier alcohol consumption [12 13], but other findings include minor or negligible differences with non-alcoholic schizophrenia patients [14]. Specific deficits reported to be worse among dual-diagnosis patients include verbal and working memory, executive functioning, set-shifting, and planning, as well as facial-recognition [12 13]. Potential confounding effects in such studies include the impact of acute psychotic illness or recent alcohol-abuse or withdrawal, as well as limited sensitivity of some assessment methods used for this purpose [12-14].

Efforts to improve methods of assessing cognitive dysfunctions in psychotic-disorder patients include the U.S. National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia

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(MATRICS) battery of tests addressing processing speed, attention-vigilance, working memory, verbal learning, visual learning, problem solving and social cognition [15]. We previously used the relatively rapid and sensitive, validated, Italian-language, Milan Overall Dementia Assessment (MODA) battery [16] to compare cognition in treated, stable, adult schizophrenia outpatients and matched healthy controls: schizophrenia patients were far more impaired (Odds Ratio [OR] = 12.0 [95% CI: 3.87-37.2]), as expected [17]. We now report on further use of this method to compare cognitive functions among well-matched schizophrenia patients with and without co-morbid alcohol abuse, and against matched healthy control subjects.

Materials and Methods

Aim and subjects

We compared cognitive performance among schizophrenia patients with *versus* without alcohol abuse, and both to healthy controls. All participants provided informed consent following approval of the protocol by a local ethics review committee. The study was performed in accordance with the principles of the 1983 Declaration of Helsinki. Patient-subjects screened were consecutive, adult outpatients diagnosed with schizophrenia by DSM-IV-TR criteria (based on consensus of two senior clinical investigators [AL and AB]). Patients had been ill for 17.9 ± 8.71 years, received clinically determined treatments (75% received atypical antipsychotics and 25% received older neuroleptics or drug-combinations), were considered clinically stable when studied, and had not been hospitalized for at least two years. In addition, the dual-diagnosis cases also met DSM-IV-TR criteria for lifetime diagnoses of alcohol abuse, confirmed with total scores of ≥ 6 on the revised Michigan Alcohol Screening Test (MAST [18]). Subjects had never experienced alcohol-withdrawal reactions, were not intoxicated when evaluated, and had no clinically significant general medical or neurological disorders. We compared these patients to 21 healthy adults matched for sex, age and educational background.

Assessments

Cognitive functioning was evaluated with the Milan Overall Dementia Assessment (MODA) scale [16 17]. This method requires approximately 40 min to administer and has yielded superior sensitivity and specificity to the Mini Mental State Examination (MMSE) in dementia patients, and addresses the same cognitive domains as the much longer MATRICS battery [15 16]. The MODA scale includes three sections: [a] *orientation* (temporal, spatial, personal and family, with subtotal scores ranging from 0 to 35); [b] *autonomy* (eating, walking, dressing, personal hygiene and sphincter-control, with potential subtotal scores of 0-15), and [c] a battery of *brief neuropsychological tests* (assessing attention, intelligence, memory, language, as well as spatial and visual perception, to yield subtotals of 0-50). Total scores (MODA*t*) can range from 0 to 100, and are numerically adjusted for age and years of education to yield MODA*a* (adjusted) scores; final MODA*a* scores are classified as *normal* (> 89.0), *borderline* (89.0-85.5), or *definitely impaired* (< 85.5 [16]).

We used the 25-item revised Michigan Alcohol Screening Test (MAST) questionnaire to verify the presence of lifetime alcohol abuse. It is sensitive and virtually unique among alcohol assessment instruments for having been validated with Italian patients [18]. MAST total scores can range from 0-2 (no clinically significant alcohol abuse), to 3-5 (mild-moderate abuse), and ≥ 6 (severe abuse or dependence). We also rated overall psychopathology with the *Positive and Negative Syndrome Scale* (PANSS [19]), including items recommended by Andreasen et al. [20] to assess remission in schizophrenia (Table I).

Data analysis

Statistical analyses employed Statview-5® software (SAS Institute, Cary, NC). MODA test results adjusted for age and education provided MODA*a* scores for statistical comparisons. Data are presented as means ± standard deviations (SD) or values with 95% confidence intervals (CI). Continuous data were compared by single or multiple factor ANOVA (*t*), and categorical data with contingency tables (χ^2), and Pearson linear correlations (*r*) compared MAST ratings with cognition among comorbid patients. Findings were considered statistically significant with two-tailed $p \leq 0.01$ to compensate for multiple comparisons.

Results

Sample characteristics

The 82 study subjects included 40 diagnosed with schizophrenia with no history of alcohol abuse, 17 meeting DSM-IV-TR criteria for both diagnoses, and 25 healthy controls. The subgroups compared were: [*a*] patients diagnosed with *schizophrenia* only (26 men, 14 women, aged 43.8 ± 10.8 years, educated 14.9 ± 7.03 years, with MAST scores of 2.05 ± 2.47); [*b*] *dual-diagnosis* cases (12 men, 5 women, aged 44.2 ± 10.3 years, educated 13.6 ± 7.57 years, with MAST scores averaging 14.8 ± 6.53); [*c*] 21 *healthy controls* (17 men, 8 women, aged 45.6 ± 10.4 years, with 13.8 ± 4.11 years of education and MAST scores of 0.62 ± 0.92). Although the study-subgroups were well matched for age, sex and education level, MODA*a* scores were nevertheless adjusted numerically for effects of age and education (Table I). Duration of psychotic illness was similar with *versus*

TABLE I.
Characteristics of study subjects. *Caratteristiche dei pazienti.*

Characteristic	a. Schizophrenia	b. Dual-diagnosis	c. Healthy controls
MAST score	2.05 ± 2.47	14.8 ± 6.53	0.62 ± 0.92
Current age (years)	43.8 ± 10.8	44.2 ± 10.3	43.9 ± 9.82
Sex (% men)	65.0	70.6	66.7
Years of education	14.9 ± 7.03	13.6 ± 7.57	13.8 ± 4.11
Employed (%)	72.5	64.7	76.2
Years of illness	17.1 ± 8.63	17.7 ± 9.06	–
Years of treatment	14.2 ± 7.16	13.4 ± 7.40	–
PANSS total	17.6 ± 6.15	15.0 ± 5.57	–

Dual diagnosis patients (*b*) met DSM-IV criteria for schizophrenia *and* lifetime alcohol abuse. PANSS subscales: P1 = delusions; P2 = conceptual disorganization; P3 = hallucinatory behaviour; N1 = blunted affect; N4 = passivity, apathy or social withdrawal; N6 = lack of spontaneity and decreased flow of words; G5 = mannerisms and posturing; G9 = unusual thought content. PANSS total is the sum of these subscale scores, none of which differed between the patient subgroups.

without alcohol-abuse (17.1 ± 8.63 *vs*. 17.7 ± 9.06 years, respectively; Table I). Years of treatment, employment status, and psychiatric morbidity ratings (PANSS total and subscale scores) all were well-matched for the patient-subgroups (Table I); most patients were receiving a second-generation antipsychotic drug (75%) and all comorbid patients had abused alcohol clinically significantly within the preceding 5 years.

Cognitive functioning

MODA*a* scores differed highly significantly among the three clinical groups compared (schizophrenia alone, schizophrenia with alcohol-abuse and normal controls), based on multiple ANOVA modeling ($t = 3.59$, $p < 0.0001$). These cognition scores were only 6.20% lower among subjects with *versus* without alcohol abuse (80.2 ± 10.2 *vs*. 85.5 ± 5.11), with few and non-significant differences in subscale scores, and were impaired insignificantly more often (MODA*a* scores < 85.5: 58.8% *vs*. 45.0%) among those with *vs*. without co-morbid alcohol abuse (Table II). These findings suggest that comorbid alcohol abuse accounted for only minor differences in cognitive performance among alcohol-comorbid and non-comorbid schizophrenia patients.

In contrast, as expected, overall MODA*a* scores were significantly and similarly lower in both schizophrenia patient groups than among healthy controls (groups *a* + *b* *vs*. *c*). Differences were notable in four important domains: verbal intelligence and fluency, prose memory and reversal learning (all $p \leq 0.01$; Table II).

MODA/MAST Correlations

Finally, we correlated MODA cognitive ratings and alcohol abuse scores (MAST total) for comorbid patients. These ratings of alcohol abuse were moderately but significantly correlated with MODA*a* total scores and with several subtests, ranking: total score ($r = -0.41$, slope [95% CI)]: 0.443 [-0.663 to -0.224]; $p < 0.0001$) > prose memory > token test > finger agnosia (all three $r = -0.29$ to -0.36; all $p \leq 0.001$). Nine other MODA subscale scores were not significantly correlated with MAST scores; in descending order: [a] attention, [b] reversal learning, [c] autonomy, [d] personal orientation, [e] verbal intelligence, [f] verbal fluency, [g] Street completion, [h] constructional apraxia, and [i] spatial orientation (all $r = -0.02$ to -0.20, all $p = 0.07$-0.85; not shown).

Discussion and Conclusions

The present study employed a validated testing procedure (MODA) developed and tested specifically to evaluate cognition among Italian neuropsychiatric patients. The findings add to the few and inconsistent studies that have directly compared schizophrenia patients without substance-use comorbidity to those meeting diagnostic criteria for relatively severe, lifetime alcohol abuse [10-14]. Limitations of the study include relatively small subgroups and the possibility that effects of prolonged psychotic illness (about 17 years) and possible effects of treatment dominated comparisons involving patients whose intensity or duration of alcohol abuse may have varied. However, the patient-groups and healthy controls were well-matched for sex, age, education and duration of illness, and the cognitive deficits observed were not correlated with ratings of psychotic morbidity (Table I). The MODA methods may not be adequately validated for assessing all aspects of cognitive impairments in schizophrenia patients, but it has demonstrated high specificity and sensitivity in de-

TABLE II.
Cognitive impairment in schizophrenia, dual-diagnosis patients and healthy controls. *Impairment cognitivo in pazienti affetti da schizofrenia, doppia diagnosi e in controlli sani.*

Tests	Cognitive domains	a. Schizophrenia	b. Dual-diagnosis	c. Healthy controls	p values	
					a *vs.* b	a + b *vs.* c
MAST	[Alcohol abuse]	2.05 ± 2.47	14.8 ± 6.53	0.62 ± 0.92	< 0.0001*	0.001*
MODA*a* < 85.5 (%)	Overall	45.0	58.8	19.0	0.482	< 0.0001*
MODA*a* score	Overall	85.5 ± 5.11	80.2 ± 10.2	90.9 ± 4.56	0.012*	< 0.0001*
Temporal orientation	Working memory	9.71 ± 0.84	9.01 ± 2.67	9.98 ± 0.04	0.143	0.184
Spatial orientation	Working memory	2.87 ± 0.33	2.88 ± 0.33	2.95 ± 0.21	0.939	0.338
Personal orientation	Working memory	9.72 ± 0.64	9.52 ± 0.94	10.0 ± 0.00	0.366	0.043
Family orientation	Working memory	11.7 ± 0.63	11.2 ± 1.15	11.8 ± 0.50	0.064	0.154
Autonomy scale	Social cognition, problem-solving	14.8 ± 0.36	14.5 ± 1.23	15.0 ± 0.00	0.135	0.133
Reversal learning	Verbal & visual learning	4.07 ± 1.62	3.88 ± 1.72	4.90 ± 0.43	0.689	0.017*
Attention test	Vigilance, attention	9.20 ± 1.15	8.64 ± 1.76	9.66 ± 0.43	0.167	0.049
Verbal Intelligence	Verbal learning	3.05 ± 1.51	2.70 ± 1.75	5.00 ± 1.14	0.458	< 0.0001*
Prose memory	Working memory	3.84 ± 2.64	2.65 ± 2.44	5.59 ± 1.95	0.116	0.001*
Verbal fluency	Verbal fluency	3.30 ± 1.38	3.52 ± 1.62	4.71 ± 0.64	0.588	0.0001a
Token test	Verbal learning, speed	4.91 ± 0.25	4.67 ± 0.52	4.95 ± 0.15	0.025	0.187
Finger agnosia	Processing speed	4.40 ± 0.81	3.58 ± 1.83	4.61 ± 0.74	0.023	0.116
Constructional apraxia	Processing speed	3.03 ± 0.32	3.05 ± 0.55	3.00 ± 0.00	0.857	0.621
Street completion test	Processing speed	2.27 ± 0.64	2.17 ± 0.80	2.57 ± 0.50	0.625	0.051

Comparisons are schizophrenia-only (*a*) *versus* dual-diagnosis (schizophrenia + alcohol abuse) patients (*b*) and all patients (*a* + *b*) *versus* healthy controls (*c*). Several MODA subtests showed no differences between groups *a* and *b*, or between patient groups (*a* + *b*) and controls (*c*): [a] temporal orientation, [b] spatial orientation, [c] personal orientation, [d] family orientation, [e] autonomy, [f] attention, [g] token test, [h] finger agnosia, [i] constructional apraxia and [*l*] Street completion test.
* Significantly different (two-tailed $p \leq 0.01$ to adjust for multiple comparisons).

tecting cognitive deficits, including attention, memory, intelligence, language, space cognition and visual perception, in various neuropsychiatric patients including those diagnosed with dementia and schizophrenia [17 21]. Moreover, the MODA battery explores cognitive domains involved in alcohol abuse and is relatively rapid and efficient [21 22].

Overall, the present findings suggest only minor, though statistically significant, additional cognitive impairment in a broad test-battery among DSM-IV-TR schizophrenia patients also meeting DSM-IV-TR criteria for lifetime alcohol abuse. Moreover, cognitive defects and MAST ratings for alcohol abuse were significantly correlated, indicating that more severe alcohol abuse was associated with greater cognitive deficits (Table II). It was not possible to assess effects of specific treatments since all patients received antipsychotic drugs. Finally, the comparison of schizophrenia patients to healthy controls confirmed repeated findings that schizophrenia patients show cognitive impairments, notably in verbal competence and working memory [4 5 17 23].

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