

Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis

Stéphane Potvin^{a,b}, Christian C. Joyal^{a,c,d,*}, Julie Pelletier^e, Emmanuel Stip^{a,e}

^a *Fernand-Seguin Research Center, University of Montreal, Montreal, Canada*

^b *Department of Neurosurgery, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Canada*

^c *Philippe-Pinel Institute of Montreal, Canada*

^d *Department of Psychology, University of Quebec at Trois-Rivieres, Trois-Rivieres, Canada*

^e *Louis-H Lafontaine Hospital, Department of Psychiatry, Faculty of Medicine, University of Montreal, Montreal, Canada*

Received 1 December 2006; received in revised form 20 April 2007; accepted 24 April 2007

Available online 5 July 2007

Abstract

Although a substance use disorder (SUD) is traditionally associated with psycho–bio-social impairments, recent investigations among persons with schizophrenia (Sz) generated divergent results. Certain persons with Sz+SUD might in fact present better social and cognitive functioning than persons with Sz without SUD. This meta-analysis was conducted to verify this counterintuitive possibility and to determine whether factors such as substance type, severity or nature of psychotic symptoms and age of the patients help discriminate these subgroups. Twenty-three studies met the inclusion criteria and data from 1807 persons with schizophrenia, with or without comorbid SUD, were available for analyses. As a group, persons with Sz+SUD did not obtain significantly higher scores at a Global Cognitive Index than persons with Sz without SUD, although they were better at the Trail Making Task and the speed processing domain. Secondary analyses showed the importance of considering intermediate factors, particularly the preferred substance used and the mean age. While consumption of alcohol was associated with a global cognitive scores similar to that of persons with Sz without an SUD and lower working memory capacities, preferential use of cannabis was instead associated with higher scores for problem solving and reasoning and visual memory. Age was inversely related to the size of the effects. It is concluded that previous mixed results obtained with cognitive evaluations of persons with Sz+SUD might reflect the heterogeneity of participants and that subgroups of patients might be defined on the basis of intermediate factors.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Schizophrenia; Substance abuse; Cognition; Neuropsychology; Meta-analysis

1. Introduction

Lifetime prevalence of substance use disorders (SUD) among persons with schizophrenia (Sz) approaches 50%

(Kavanagh et al., 2002; Regier et al., 1990). Substance use and abuse are commonly reported as a mean to alleviate distress and painful affect by the patients (e.g. Dixon et al., 1990), and negative-type symptoms such as blunted affect, dysphoria, social isolation, and poor interpersonal skills represent risk factors for an SUD within this population (see Mueser et al., 1998 for an overview). These factors are associated with lower level of general functioning, less years of education, more neurological

* Corresponding author. University of Quebec at Trois-Rivieres, Department of Psychology, 3351 des Forges, C.P. 500, Trois-Rivieres, Quebec, Canada G9A 5H7. Fax: +1 819 376 5210.

E-mail address: christian.joyal@uqtr.ca (C.C. Joyal).

soft signs, poorer prognosis and inferior cognitive capacities among persons with Sz (e.g. Andreasen et al., 1990; Buchanan et al., 1990; Merriam et al., 1990; Fenton and McGlashan, 1991; Kelley et al., 1992; Gupta et al., 1995). Paired with the neurotoxic effects of sustain substance use, these SUD-related factors underlie the intuitive and traditional conception that SUD are associated with more cognitive deficits among persons with Sz, just as it is observed in the general population (e.g. Scheurich, 2005). However, conclusions from recent studies diverged and cognitive profile of persons with the dual diagnosis of Sz+SUD is heterogeneous, as lower (Serper et al., 2000a,b; Sevy et al., 1990), similar (Addington and Addington, 1997; Cleghorn et al., 1991; Nixon et al., 1996; Pencer and Addington, 2003) and better (Carey et al., 2003; Joyal et al., 2003; Potvin et al., 2005; Stirling et al., 2005; McCleery, Addington, and Addington, 2006) performances have been observed as compared with persons with Sz without an SUD. The first objective of this meta-analysis was to determine to which extent better cognitive functioning is found among persons with Sz+SUD.

Consideration of potentially important factors might be helpful to clarify the picture. For instance, some investigations reported higher levels of premorbid or current social functioning, lower severity of negative symptoms and lesser global severity of illness than average for persons with Sz+SUD (Arndt et al., 1992; Breakey et al., 1974; Buckley et al., 1994; Dixon et al., 1991; Kirkpatrick et al., 1996; Mueser et al., 1990; Ritzler et al., 1977; Salyers and Mueser, 2001; Sanguineti and Samuel, 1993; Tsuang et al., 1982; Zisook et al., 1992). It has been speculated that in these cases, the probability of first and subsequent contacts with drugs, especially if illegal, is superior because social functioning is better (Arndt et al., 1992; Joyal et al., 2003). Better social functioning, in turn, is associated with higher cognitive capacities among persons with Sz (e.g. Silverstein et al., 2002). Thus, intermediate factors such as functional outcome, severity of negative symptoms, the nature of the preferred type of drug (alcohol vs. illegal; mild vs. hard), and age of the patients might be relevant in discriminating neuropsychological profiles.

A second goal of this study was to explore the usefulness of considering intermediate factors to discriminate levels of cognitive functioning among persons with Sz+SUD. Because older patients (especially with a longer history of SUD) might present poorer cognitive functioning than younger patients, and based on the assumption that better social functioning is associated with illegal drug consumption, it was hypothesized that younger patients who misuse illegal drugs would present

better neuropsychological capacities than average among persons with Sz.

2. Methods

2.1. Search

A search in computerised literature databases (PubMed and PsycInfo) was conducted, using the following keywords: “schizophrenia” and “alcohol” or “amphetamine” or “cannabis” or “cocaine” or “hallucinogens” or “heroin” or “marijuana” or “phencyclidine” and “cognition”. Studies were also identified by cross-referencing of included studies. A consensus has been reached between authors on the studies retained or discarded, based on the following inclusion and exclusion criteria (only published studies were included).

2.2. Study selection

Inclusion criteria were: 1) Patients with a schizophrenia spectrum disorder: schizophrenia, schizoaffective disorder or schizophreniform disorder; 2) Schizophrenia patients with and without a comorbid SUD (abuse or dependence); 3) Psychoactive substances: alcohol, amphetamines, cannabis, cocaine, hallucinogens, heroin or phencyclidine (PCP); 4) Cognitive functioning measured with validated neuropsychological tests; 5) Studies published before August 31st 2006. Exclusion criteria were: 1) Patients with an affective (bipolar/unipolar) psychotic disorder and patients suffering from toxic psychoses; 2) Schizophrenia patients exclusively addicted to tobacco or benzodiazepines.

2.3. Data extraction and quantitative data synthesis

2.3.1. Considering confounding factors

Differences between the groups in symptomatology and age were first assessed because they might differ across studies and underlie divergent neuropsychological profiles. Scores at the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS) or the Scales for the Assessment of Positive (SAPS) or Negative (SANS) Symptoms were separately pooled for the SZ+SUD and SZ participants when available. Sex ratio was also considered since SZ+SUD patients are commonly younger and more likely to be male than SZ patients (Ries et al., 2000; Swofford et al., 2000). Relevant data (*N*, mean and SD) of the SZ+SUD and the SZ groups from each study were pooled using D-STAT (Johnson, 1989). For symptoms and age independent 2-sample *T* tests were performed. For sex, a

chi-square test was applied. These were collapsed using *D*-STAT.

2.3.2. Global cognitive index

Two reviewers (SP and JP) independently extracted the data and disagreements were resolved with discussion. Using Comprehensive Meta-Analysis (Borenstein and Rothstein, 1999), effect size estimates of the differences in cognitive scores (mean and standard deviation) between Sz+SUD and SZ patients were calculated [Note: For the Stirling et al. (2005) study, the effect size estimates were calculated from *p*-values]. Within a random effect model, a composite effect size estimate for the whole set of studies (Global Cognitive Index) was derived using Hedges' *g* (Cooper and Hedges, 1994), which provides an effect size adjusted for sample size. Random effect models, being more stringent than fixed effect models, allow population-level inferences (DerSimonian and Laird, 1986). The direction of the effect size was positive for better performance and negative for poorer performance from SZ+SUD patients compared with SZ patients. Following the convention of Cohen (1988), effect sizes of 0.2, 0.5 and 0.8 were considered small, moderate and large, respectively.

2.4. Specific neuropsychological tasks and cognitive functions

Because neuropsychological investigations typically involve multiple cognitive measures, a global cognitive index was created by aggregating effect size estimates of each score derived from each cognitive test, resulting in a mean effect size estimate of general cognitive functioning for each study. Additional analyses were performed for specific cognitive measures (California Verbal Learning Task, CVLT, Controlled Oral Word Association Test, COWAT, Continuous Performance Task, CPT; Stroop, Trail Making Task A and B (TMT), Weschler Adult Intelligence Scale, WAIS; Weschler Memory Scale, WMS and the Wisconsin Card Sorting Task, WCST) and broad cognitive functions. The broad categories were derived from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative of the National Institute of Mental Health (Green et al., 2004; Nuechterlein et al., 2004; see also www.matrics.ucla.edu). Based on 13 factor analytic studies of cognitive performance in schizophrenia, the MATRICS group concluded that 6 separable cognitive domains were more likely to be impaired among persons

Table 1
The NIMH–MATRICS cognitive domains

Cognitive domain	Cognitive tests identified by MATRICS	Other similar cognitive tests
Working memory	WMS Spatial Span WAIS Letter–Number Sequencing Spatial Delayed Response Task Arithmetic	CANTAB Spatial Working Memory CANTAB Spatial Span ACT DSDT (non-distraction) Spatial Block Span SPAN
Attention/vigilance	Continuous Performance Test	
Verbal learning and memory	WMS (Logical Memory and Verbal Paired Associates) California Verbal Learning Test Hopkins Verbal Learning Test	Rey Verbal Learning Test VET (recall) CANTAB Pattern Recognition Memory
Visual learning and memory	WMS (Family Pictures and Visual Reproduction)	CANTAB Paired Associates Learning Rey Complex Figure (recall)
Reasoning and problem solving	WAIS Block Design WAIS Matrix reasoning WAIS Picture Completion WAIS Picture arrangement Tower of London Wisconsin Card Sorting Test	CANTAB Stockings of Cambridge Porteus Mazes Test
Speed of processing	COWAT Trail Making A/B (time) Grooved Pegboard Test WAIS Digit Symbol-Coding Symbol Digit Modalities Test Stroop Test	CANTAB Motor Screening Chicago Word Fluency Test Jones–Gotman Design Fluency Finger Tapping Test SOA (psychomotor rate) Pin Test

ACT = Auditory Consonant Trigrams Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; COWAT = Controlled Oral Word Association Test; DSDT = Digit Span Distraction Task; SOA = Span of Attention Test; SPAN = Forced-choice Span of Apprehension Task; VET = Verbal Encoding Test; WAIS = Weschler Adult Intelligence Scale; WMS = Weschler Memory Scale.

with schizophrenia (attention, speed processing, verbal learning and memory, visual learning and memory, reasoning and problem solving, and working memory; see Table 1). They also identified a series of tests loading

for these cognitive domains (Table 1). Studies considered in this meta-analysis used various cognitive tests, including measures not comprised in the MATRICS' guidelines. These cognitive tests were also classified in

Table 2
Cross-sectional studies of single and dual diagnosis schizophrenia patients assessed for cognition

Authors	PAS type	N	Psychosis scale	Cognitive tests ^a
Addington and Addington (1997)	Mixed	66	PANSS	Chicago Word Fluency Test; CPT; Jones–Gotman Design Fluency Test; Rey Complex Figure; SPAN; WAIS-Revised; WCST
Allen et al. (1999)	Alcohol	271	No measure	HRNB; WAIS; WRAT
Barnes et al. (2006)	Mixed	152	SANS SAPS	CANTAB PRM, SOC, SSP and SWM; NART, WAIS-revised
Bowie et al. (2005)	Alcohol	35	PANSS	COWAT; RAVLT; UPSA; WAIS-III; WRAT-3rd edition
Carey et al. (2003)	Mixed (alcohol)	56	No measure	Benton Visual Retention Test; COWAT; Stroop Test; Grooved Pegboard Test; Rey Complex Figure; Symbol Digit Modalities Test; TMT; WAIS-Revised; WCST
Cleghorn et al. (1991)	Mixed	63	SADS	Continuous Reaction Time; COWAT; Grooved Pegboard Test; Porteus Mazes Test; Rey Complex Figure Test; Spatial Block Span; TMT; WAIS; WCST
Cooper et al. (1999)	Cocaine	49	BPRS	CPT; CVLT; Pin Test; WCST
Copersino et al. (2004)	Cocaine	42	No measure	CVLT; Stroop
Herman (2004)	Mixed	89	BPRS ^b	COWAT; Stroop Color Word Test; TMT; WAIS-III; WMS-III
Joyal et al. (2003)	Mixed (cannabis)	30	PANSS	COWAT; Go/no-go Reaction Task; Rey Complex Figure; TMT; WAIS-Revised; WCST
McCleery et al. (2006)	Mixed	183	PANSS ^c	COWAT; CPT; Grooved Pegboard; NART; RAVLT; Rey Complex Figure; SPAN; TMT; WCST; WMS-Revised
Mohamed et al. (2006)	Alcohol	272	PANSS	CVLT; Mattis Dementia Rating Scale; WMS-Revised
Nixon et al. (1996)	Alcohol	26	No measure	Face Recognition Test; TMT
Potvin et al. (2005)	Mixed (cannabis)	76	PANSS	CANTAB MOT and PAL
Serper et al. (2000a)	Cocaine	76	No measure	CVLT
Serper et al. (2000b)	Cocaine	56	No measure	CPT; CVLT; DSDT; WCST
Sevy et al. (2001)	Mixed	118	SADS SANS	Tests regrouped into cognitive functions (language, executive, attention, memory, motor, visuospatial and IQ) (see Bilder et al., 2000)
Sevy et al. (1990)	Cocaine	51	PANSS	SOA; VET; WAIS-Revised
Smelson et al. (2003)	Cocaine	47	PANSS	COWAT; Grooved Pegboard Test; Stroop Test; Symbol Digit Modalities Test; TMT; WAIS-III; WCST
Smelson et al. (2002)	Cocaine	33	PANSS ^c	Grooved Pegboard Test; Stroop Test; Symbol Digit Modalities Test; TMT; WAIS-III; WCST
Stirling et al. (2005)	Cannabis	63	SANS ^d SAPS ^d	WAIS
Thoma et al. (2006)	Alcohol	18	PANSS ^c SANS ^c	ACT; CPT; TMT; WMS-Revised

ACT = Auditory Consonant Trigrams Test; CANTAB = Cambridge Neuropsychological Tests Automated Battery; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; DSDT = Digit Span Distraction Task; HRNB = Halstead–Reitan Neuropsychological Test Battery; MOT = Motor Screening Task (CANTAB); NART = National Adult Reading Test; PAL = Paired Associated Learning Task (CANTAB); PANSS = Positive and Negative Syndrome Scale; PAS = psychoactive substance; PRM = Pattern recognition Memory Task (CANTAB); RAVLT = Rey Auditory Verbal Learning Test; SADS = Schedule for Affective Disorders and Schizophrenia; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SOA = Span of Attention Test; SOC = Stockings of Cambridge Task (CANTAB); SPAN = Forced-Choice Span of Apprehension Task; SSP = Spatial Span Task (CANTAB); SWM = Spatial Working Memory Task (CANTAB); TMT = Trail Making Test; UPSA = UCSD Performance-Based Skills Assessment; VET = Verbal Encoding Test; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale; WRAT = Wide Range Assessment Test.

^a The sub-scores for each cognitive test are not necessarily reported in the articles.

^b Non-parametric test.

^c Data not reported.

^d Baseline assessment, whereas cognition was measured after follow-up.

the 6 MATRICS cognitive domains, based on their similarities with the tests recommended by MATRICS, given a consensus could be reached between SP and JP (see Table 1).

2.5. Secondary analyses

Secondary analyses were conducted to determine the potential interaction between the types of PAS (Psychoactive Substance) used and the cognitive scores. Studies were divided according to the preferred or basic PAS used by their participants: alcohol ($N=7$), cannabis ($N=3$), cocaine ($N=7$) or mixed ($N=6$; use of various drugs with no clear preference). Scores obtained in different cognitive categories were compared as a function of each type of preferred PAS.

Finally, a meta-regression analysis was performed using effect size estimates as dependent variables and age of the patients (mean age of both groups) as the regressor. This analysis would reveal any effect of age on the effect size. It is hypothesized that the greater the mean age (and, it is assumed, the history of substance use), the smaller would be the difference in cognitive functioning between the groups (the effect size).

3. Results

3.1. Study characteristics

A total of 228 studies were first identified, of which 200 were discarded after consulting the abstract and/or the article (for more details, see Potvin et al., 2005). Twenty-eight publications met the aforementioned search criteria from which six were excluded for the following reasons: reports from Krysta et al. (2005) and Allen and Remy (2000) were published as abstracts reporting incomplete data for meta-analytic treatment; Pencer and Addington (2003) did not specify cognitive results (authors were unsuccessfully contacted to gather missing data); Kumra et al. (2005) reported data incomplete for meta-analytic treatment; Allen et al. (2000) used a neurological exam to measure cognition instead of standardized neuropsychological tests; and the report from Liraud and Verdoux (2002) involved psychosis patients and unipolar/bipolar affective patients). Data from Mohamed et al. (2006) were treated as 2 investigations since their SZ+SUD and SZ groups were sub-divided into younger and older patients. Thus, 22 articles–23 studies — were available for this meta-analysis, with a total sample size of at least 1870 schizophrenia patients (789 SZ+SUD and 1106 SZ; see Tables 2 and 3) [Note: The Stirling et al. (2005) study comprised psychosis patients (schizophrenia-spectrum

Table 3
Composite effect size estimates (global cognitive index)

Authors	Subjects (<i>n</i>)	Hedges' <i>g</i>	Lower limit	Upper limit	<i>p</i> -value
Addington	66	-0.067	-0.544	0.410	0.782
Allen	271	-0.254	-0.552	0.044	0.094
Barnes	152	0.020	-0.334	0.374	0.912
Bowie	35	-0.743	-1.413	-0.072	0.030
Carey	56	0.615	0.021	1.210	0.042
Cleghorn	63	-0.040	-0.538	0.459	0.877
Cooper	49	-0.141	-0.693	0.411	0.617
Copersino	43	0.082	-0.514	0.679	0.787
Herman	86	0.304	-0.110	0.719	0.150
Joyal	30	0.866	0.134	1.597	0.020
McCleery	183	0.259	-0.031	0.549	0.080
Mohamed-y	136	0.329	-0.055	0.713	0.093
Mohamed-o	136	-0.098	-0.604	0.407	0.703
Nixon	26	0.272	-0.476	1.020	0.476
Potvin	76	0.324	-0.130	0.777	0.162
Serper-2000a	76	-0.413	-0.865	0.040	0.074
Serper-2000b	56	-0.274	-0.810	0.262	0.316
Sevy-2001	118	0.249	-0.179	0.677	0.253
Sevy-1990	51	0.058	-0.524	0.641	0.845
Smelson-2003	47	-0.018	-0.580	0.545	0.951
Smelson-2002	33	0.593	-0.088	1.274	0.088
Thoma	18	-0.563	-1.354	0.227	0.162
Composite	1807	0.060	-0.079	0.199	0.394

o = old; y = young.

and bipolar affective). It was excluded from the composite analysis but was included in secondary analyses].

3.2. Symptomatology, age and gender

Thirteen studies reported symptomatology scores with one or more scales (BPRS, PANSS or SAPS; Table 2). Overall, no significant difference was found between the groups. Seven of the studies reported the Positive and Negative Syndrome Scale (PANSS) scores of patients and no significant differences emerged between the SZ+SUD and SZ groups for positive (SZ+SUD group: $N=203$; PANSS-positive score= 18.8 ± 3.0 ; SZ group: $N=374$; PANSS-positive score= 17.8 ± 4.4 ; $t=0.484$; $p=0.636$) and negative symptoms (SZ+SUD group: PANSS-negative score= 18.6 ± 4.0 ; SZ group: $N=154$; PANSS-negative score= 19.8 ± 5.6 ; $t=-0.490$; $p=0.632$). Two studies used the Schedule for Affective Disorders and Schizophrenia (SADS) and no significant differences emerged between the SZ+SUD and SZ groups (SZ+SUD group: $N=65$; SADS score= 2.1 ± 0.8 ; SZ group: $N=116$; SADS score: 2.1 ± 0.9 ; $t=-0.052$; $p=0.963$). Two studies reported the scores of the Scale for the Assessment of Negative Symptoms (SANS) and no significant differences were identified between the SZ+SUD and SZ groups (SZ+SUD group: $N=137$; SANS

Table 4
Type of « predominant » psychoactive substances

PAS	Studies	Subjects	Hedges' <i>g</i>	Lower limit	Upper limit	<i>p</i> -value
Alcohol	7	608	−0.042	−0.325	0.240	0.769
Cannabis	3 ^a	169	0.571	−0.249	0.893	0.001
Cocaine	7	355	−0.069	−0.294	0.156	0.547
Mixed	6	668	0.177	−0.008	0.345	0.040

PAS = psychoactive substance; including Carey et al. (2003).

^a Including Joyal et al. (2003) and Potvin et al. (2005).

score = 1.4 ± 1.4 ; SZ group: $N=133$; SANS score = 1.5 ± 1.6 ; $t=-0.091$; $p=0.936$). Finally, one study reported data from the SAPS (Barnes et al., 2006) and another from the BPRS (Cooper et al. (1999) and none reported significant differences between SZ+SUD and SZ patients.

Twenty reports also specified the mean age of participants and no differences were observed between the groups (SZ+SUD group: $N=627$; $38.2 \text{ years} \pm 10.1$; SZ group: $N=917$; 38.5 ± 10.0 ; $t=-0.083$; $p=0.935$). Sex ratio was provided in 19 studies and significantly more males were included in the SZ+SUD group than in the SZ group (SZ+SUD group: $N=628$; 528 males (84.1%); SZ group: $N=899$; 680 males (75.6%); $\chi^2=15.924$; $p=0.0001$).

3.3. Global cognitive index

Twenty-one articles (22 studies) were included in the composite analysis (global cognitive index). Within a random-effect model, the effect size estimate was not significant (Hedges' $g=0.061$, $p=0.39$; Table 3). The effect size estimate remained non-significant after the inclusion of the study from Stirling et al. (2005) with schizophrenia-spectrum and bipolar diagnoses (Hedges' $g=0.089$; CI — 0.055 to 0.233; $p=0.225$).

3.4. Specific neuropsychological tasks and cognitive functions

Among specific neuropsychological measures, only the Trail Making Task generated significant (positive)

effect sizes (version A: Hedges' $g=0.506$, $p=0.0001$; and version B: Hedges' $g=0.524$, $p=0.0001$). No significant effect size estimates were found for CVLT, COWAT, CPT, Stroop, WAIS, WCST and WMS (not shown). As for the broad cognitive domains, only speed processing distinguished the groups with a significant, small positive effect size estimate of 0.211 (based on 16 studies and 1245 participants; see Table 5). None of the other cognitive categories (attention, problem solving and reasoning, verbal learning and memory, visual learning and memory, working memory) produced significant effect size estimates between the groups (not shown).

3.5. PAS type

Analyses conducted with the preferred PAS type (alcohol, cannabis, cocaine or mixed) revealed no significant effect size for alcohol or cocaine, with small positive significant effect size estimates for cannabis and mixed categories (Hedges' $g=0.571$, $p=0.001$ and 0.177 , $p=0.04$, respectively; Table 4). The direction of the effects might be noteworthy, being negative for alcohol and cocaine and positive for cannabis and mixed categories.

3.6. Specific cognitive domains and PAS type

While a negative, significant and moderate effect size emerged for alcohol use (working memory domain), the opposite was observed for cannabis use (for problem solving and reasoning and visual memory domains; Table 5). No significant difference was found for any cognitive functions when cocaine was preferentially used.

3.7. Age as a predictor

Meta-regression analyses revealed significant effects of age as a predictor for the effect size estimates of the global cognitive index (21 studies; $\beta=-0.011$; $p=0.040$) (Fig. 1). The same applied to the speed processing (15

Table 5
PAS type and cognitive functions *

PAS	Function	Studies	Subjects	Hedges' <i>g</i>	Lower limit	Upper limit	<i>p</i> -value
All	Speed processing	16 ^a	1245	0.211	0.013	0.409	0.037
Alcohol	Working memory	3	324	−0.415	−0.799	−0.031	0.034
Cannabis	Problem solving and reasoning	2	99	0.789	0.366	1.212	0.0001
Cannabis	Visual memory	2	145	0.446	0.100	0.791	0.011

PAS = psychoactive substance; * Only significant results are shown, Carey et al. (2003), Joyal et al. (2003) and Potvin et al. (2005) were classified as cannabis studies.

^a Without outlier study (Thoma et al., 2006) identified by funnel plot (Q -test for heterogeneity).

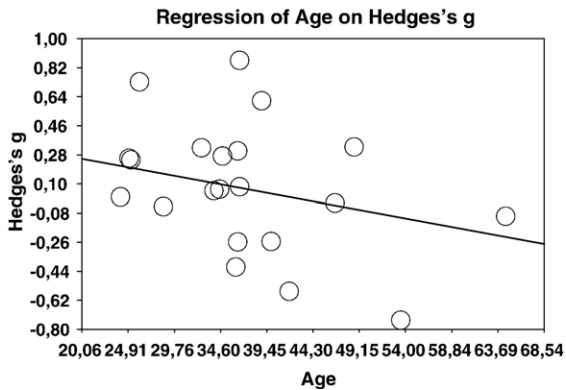


Fig. 1. Age of patients as a predictor for effect size estimates of composite cognitive index.

studies; $\beta = -0.029$; $p = 0.001$) and working memory (10 studies; $\beta = -0.034$; $p = 0.0001$) domains.

4. Discussion

Although substance abuse is traditionally associated with cognitive deficits or decline among persons with or without a mental illness, the relationship seems to be more complex in the case of Sz. An increasing number of studies unexpectedly concluded that some persons with Sz and an SUD might even show better cognitive capacities than persons with Sz without an SUD (Carey et al., 2003; Joyal et al., 2003; Potvin et al., 2005; Stirling et al., 2005; McCleery, Addington, and Addington, 2006). The main goal of this meta-analysis was to review neuropsychological investigations conducted among persons with Sz and SUD to determine to which extent better functioning might be found. A secondary objective was to determine whether intermediate variables such as age, specific domain or preferred substance type might be associated with these better cognitive patterns.

The first result of the meta-analysis is that no difference emerged between the groups (Sz and Sz+SUD) for the global cognitive index. Thus, considered as a group, participants with Sz obtained similar estimates of overall cognitive capacities, irrespective of an additional SUD. This result reinforces the notion that divergent cognitive profiles, from poorer to better, are found in association with SUD among persons with Sz. A null finding would simply reflect the additive cancellation of these diverse performances. The second finding was more unexpected: Among 8 classical neuropsychological measures, only the Trail Making Task (TMT versions A and B) discriminates between the groups; participants with Sz+SUD obtaining better results than participants with Sz. The TMT is, above

all, a test of visual scanning and visuomotor speed (Lezak, Howieson, and Loring, 2004). A significant difference between time to complete versions A and B would have indicated difficulties in more complex conceptual tracking (alternate between letters and numbers in version B), although it was not the case here. Thus, when participants with Sz and those with Sz+SUD are opposed, the only significant neuropsychological difference to emerge was for visuomotor speed, in favour of the latter group. Similarly, the only cognitive domain to distinguish the groups was speed processing. This result seems to indicate that when superior cognitive performance are observed among persons with Sz+SUD considered as a group, they might reflect better basic, general processing.

The third finding underlies the facts that persons with Sz+SUD do not represent a homogeneous group and that future investigations should consider intermediate factors to define subgroups. It suggests that at least two factors, the type of preferred substance used and the mean age of the participants, might discriminate between better and poorer cognitive functioning among persons with Sz+SUD. Exclusive use of alcohol was associated with a mean global cognitive score similar to that of persons with Sz without an SUD, while preferential uses of cannabis or mixed substances were associated with significantly higher global cognitive scores. In particular, cannabis users obtained significantly better results in the domains of problem solving and reasoning and visual memory. On the contrary, exclusive use of alcohol was associated with significantly lower scores on working memory tasks. No difference was observed for cocaine users, although chronic use of cocaine is usually associated with the worse neuropsychological performance (e.g. Serper et al., 2000a,b; Sevy et al., 1990) and should be considered separately in future studies. Besides, age represented a moderating factor in this meta-analysis, as the effect sizes of the Global Cognitive Index, the speed processing and the working memory domains significantly decreased with increased age. Thus, the preferred type of substance used, the mean age, the nature and severity of negative symptoms and the associated level of social functioning (rarely reported in existing studies) represent factors to be controlled in future investigations. An interaction between age and cognitive functioning might also be found among persons with Sz+SUD, which deserves further investigation (Allen et al., 1999). Significantly more males than females were also found in the groups of Sz+SUD, as expected, although there is no reason to believe that males would perform better than females in this population (Goldstein et al., 1998).

These results concord with the aforementioned hypothesis that in order to acquire and sustain an illegal drug habit, a person with schizophrenia would need better social and cognitive functioning than average. Thus, previous reports of better neuropsychological results among persons with Sz+SUD might have included this type of abuser. Two moderating factors are higher age and chronic use of cocaine or other hard drugs. It is plausible that younger patients who use cannabis would be more likely to present better cognitive functioning than persons with Sz. Another intriguing avenue is the neuroprotective action of cannabinoids, the active components of marijuana, which have been linked with prevention of diverse brain pathologies (e.g. Ramirez et al., 2005). Although purely speculative, cannabis might also have a neuroprotector effect among persons with Sz, at least under a certain age and before chronic use. In any case, it is also possible that subgroups exist among persons with Sz+SUD where older patients using exclusively alcohol, suffering more from negative symptoms and presenting low social functioning would present inferior cognitive capacities than persons with schizophrenia, who would in turn present lesser cognitive capacities than young male suffering from a predominance of positive symptoms, presenting better social functioning and using cannabis. Inclusion and exclusion of these subgroups would explain past divergence of conclusions; they should be considered by future investigations; and they would require highly different types of interventions.

Role of funding source

ES holds the Eli Lilly Chair in Schizophrenia from the University of Montreal and SP received a postdoctoral scholarship from the Fonds de recherche en Santé du Québec (FRSQ). The funding sources had no involvement in the study design; collection, analysis and interpretation of the data; writing of the report and the decision to submit it for publication.

Contributors

SP and JP managed the literature searches and analyses; SP undertook the statistical analyses; CCJ wrote the first draft of the manuscript, CCJ, SP and ES contributed to subsequent drafts and all authors approved the final version.

Conflict of Interest

There was no actual or potential conflict of interest including financial, personal or other relationships with other people or organizations.

Acknowledgment

ES is holder of the Eli Lilly Chair in Schizophrenia from the University of Montreal. SP is holder of a postdoctoral scholarship from the Fonds de recherche en Santé du Québec (FRSQ). The authors would like to thank Dr John Stirling who generously provided missing data.

References

- Addington, J., Addington, D., 1997. Substance abuse and cognitive functioning in schizophrenia. *J. Psychiatry Neurosci.* 2, 99–104.
- Allen, D.N., Remy, C.J., 2000. Neuropsychological deficits in patients with schizophrenia and alcohol dependence. *Arch. Clin. Neuropsychol.* 15, 762–763.
- Allen, D.N., Goldstein, G., Aldarondo, F., 1999. Neurocognitive dysfunction in patients diagnosed with schizophrenia and alcoholism. *Neuropsychology* 13, 62–68.
- Allen, D.N., Goldstein, G., Forman, S.D., Kashavan, M.S., van Kammen, D.P., Sanders, R.D., 2000. Neurologic examination abnormalities in schizophrenia with and without a history of alcohol. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 13, 184–187.
- Andreasen, N.C., Flaum, M., Swayze II, V.W., Tyrrell, G., Arndt, S., 1990. Positive and negative symptoms in schizophrenia. A critical reappraisal. *Arch. Gen. Psychiatry* 47, 615–621.
- Arndt, S., Tyrrell, G., Flaum, M., Andreasen, N.C., 1992. Comorbidity of substance abuse and schizophrenia: the role of pre-morbid adjustment. *Psychol. Med.* 22, 379–388.
- Barnes, T.R.E., Mutsatsa, S.H., Hutton, S.B., Watt, H.C., Joyce, E.M., 2006. Comorbid substance use and age at onset of schizophrenia. *Br. J. Psychiatry* 188, 237–242.
- Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M.J., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am. J. Psychiatry* 157, 549–559.
- Borenstein, M., Rothstein, H., 1999. *Comprehensive Meta-analysis: a computer program for research synthesis*. Biostat, Englewood, NJ.
- Bowie, C.R., Serper, M.R., Riggio, S., Harvey, P.D., 2005. Neuro-cognition, symptomatology, and functional skills in older alcohol-abusing schizophrenia patients. *Schizophr. Bull.* 31, 175–182.
- Breakey, W.R., Goodell, H., Lorenz, P.C., McHugh, P.R., 1974. Hallucinogenic drugs as precipitants of schizophrenia. *Psychol. Med.* 4, 255–261.
- Buchanan, R.W., Kirkpatrick, B., Heinrichs, D.W., Carpenter, W.T., 1990. Clinical correlates of the deficit syndrome of schizophrenia. *Am. J. Psychiatry* 147, 290–294.
- Buckley, P.B., Thompson, P., Way, L., Meltzer, H.Y., 1994. Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for Clozapine therapy. *Am. J. Psychiatry* 151, 385–389.
- Carey, K.B., Carey, M.P., Simons, J.S., 2003. Correlates of substance use disorder among psychiatric outpatients: focus on cognition, social role functioning, and psychiatric status. *J. Nerv. Ment. Dis.* 191, 300–308.
- Cleghorn, J.M., Kaplan, R.D., Szechtman, B., Szechtman, H., Brown, H.G., Franco, S., 1991. Substance abuse and schizophrenia: effect on symptoms but not on neurocognitive function. *J. Clin. Psychiatry* 52, 26–30.
- Cohen, J., 1988. *Statistical Power Analysis for the Behavioral Sciences* 2nd ed. Erlbaum, Hillsdale, NJ.
- Copersino, M.L., Serper, M.R., Vadhan, N., Goldberg, B., Richarme, D., Chou, J.C.Y., Stitzer, M., Cancro, R., 2004. Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Res.* 128, 209–218.
- Cooper, H., Hedges, L.V. (Eds.), 1994. *Handbook of Research Synthesis*. Russell Sage Foundation, New York.
- Cooper, L., Liberman, D., Tucker, D., Neuchterlein, K.H., Tsuang, J., Barnett, H.L., 1999. Neurocognitive deficits in the dually diagnosed

- with schizophrenia and cocaine abuse. *Psychiatr. Rehabil. Skills* 3, 231–245.
- DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control. Clin. Trials* 7, 177–188.
- Dixon, L., Haas, G., Weiden, P., Sweeney, J., Frances, A., 1990. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. *Schizophr. Bull.* 16, 69–79.
- Dixon, L., Haas, G., Weiden, P.J., Sweeney, J., Frances, A.J., 1991. Drug abuse in schizophrenic patients : clinical correlates and reasons for use. *Am. J. Psychiatry* 148, 224–230.
- Fenton, W.S., McGlashan, T.H., 1991. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Arch. Gen. Psychiatry* 48, 978–986.
- Goldstein, J.M., Seidman, L.J., Goodman, J.M., Koren, D., Lee, H., Weintraub, S., Tsuang, M.T., 1998. Are there sex differences in neuropsychological functions among patients with schizophrenia. *Am. J. Psychiatry* 155, 1358–1364.
- Green, M.F., Nuechterlein, K.H., Gold, J.M., Barch, D.M., Cohen, J., Essock, S., Fenton, W.S., Goldberg, T.E., Heaton, R.K., Keefe, R.S.E., Kern, R.S., Stover, E., Weinberger, D.R., Zalcman, S., Marder, S.R., 2004. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH–MATRICS conference to select cognitive domains and test criteria. *Biol. Psychiatry* 56, 301–307.
- Gupta, S., Rajaprabhakaran, P., Arndt, S., Flaum, M., Andreasen, N., 1995. Premorbid adjustment as a predictor of phenomenological and neurobiological indices in schizophrenia. *Schizophr. Res.* 16, 189–197.
- Herman, M., 2004. Neurocognitive functioning and quality of life among dually-diagnosed and non-substance abusing schizophrenia in patients. *Int. J. Ment. Health Nursing* 13, 282–291.
- Johnson, B.T., 1989. *DSTAT: software for the meta-analytic review of research literatures*. Lawrence Erlbaum Associates, Hillsdale, NJ.
- Joyal, C.C., Hallé, P., Lapierre, D., Hodgins, S., 2003. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophr. Res.* 63, 297–299.
- Kavanagh, D.J., McGrath, J., Saunders, J.B., 2002. Substance misuse in patients with schizophrenia: epidemiology and management. *Drugs* 62 (5), 743–755.
- Kelley, M.E., Gilbertson, M., Mouton, A., van Kammen, D.P., 1992. Deterioration in premorbid functioning in schizophrenia: a developmental model of negative symptoms in drug-free patients. *Am. J. Psychiatry* 149, 1543–1548.
- Kirkpatrick, B., Amador, X.F., Flaum, M., Yale, S.A., Gorman, J.M., Carpenter Jr., W.T., Tohen, M., McGlashan, T., 1996. The deficit syndrome in the DSM-IV Field Trial: I. Alcohol and other drug abuse. *Schizophr. Res.* 20, 69–77.
- Krysta, K., Krupka-Matuszczyk, I., Klaslik, A., 2005. Impact of drug abuse on cognitive functioning in schizophrenia. *Eur. Neuropsychopharmacol.* 15 (Suppl 3), S579.
- Kumra, S., Thaden, E., DeThoma, C., Kranzler, H., 2005. Correlates of substance abuse in adolescents with treatment-refractory schizophrenia and schizoaffective disorder. *Schizophr. Res.* 73, 369–371.
- Lezak, M.D., Howieson, D.B., Loring, D.W. (Eds.), 1994. *Neuropsychological Assessment*, 4th ed. Oxford University Press, New York.
- Liraud, F., Verdoux, H., 2002. Impact neuropsychologique de l'abus de substances psychoactives dans les troubles psychotiques et de l'humeur. *Encephale* 28, 160–168.
- McCleery, A., Addington, J., Addington, D., 2006. Substance misuse and cognitive functioning in early psychosis: a 2 year follow-up. *Schizophr. Res.* 88, 187–191.
- Merriam, A.E., Kay, S.R., Opler, L.A., Kushner, S.F., van Praag, H.M., 1990. Neurological signs and the positive–negative dimension in schizophrenia. *Biol. Psychiatry* 28, 181–192.
- Mohamed, S., Bondi, M.W., Kasckow, J.W., Golshan, S., Jeste, D.V., 2006. Neurocognitive functioning in dually diagnosed middle aged and elderly patients with alcoholism and schizophrenia. *Int. J. Geriatr. Psychiatry* 21 (8), 711–718.
- Mueser, K.T., Yarnold, P.R., Levinson, D.F., Singh, H., Bellack, A.S., Kee, K., Morrison, R.L., Yadam, K.G., 1990. Prevalence of substance abuse in schizophrenia : demographic and clinical correlates. *Schizophr. Bull.* 16, 31–56.
- Mueser, K.T., Drake, R.E., Wallach, M.A., 1998. Dual diagnosis: a review of etiological theories. *Addict. Behav.* 23, 717–734.
- Nixon, S.J., Hallford, G.H., Tivis, R.D., 1996. Neurocognitive function in alcoholic, schizophrenic, and dually diagnosed patients. *Psychiatry Res.* 64, 35–45.
- Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. *Schizophr. Res.* 72 (1), 29–39.
- Pencer, A., Addington, J., 2003. Substance use and cognition in early psychosis. *J. Psychiatry Neurosci.* 8, 48–54.
- Potvin, S., Briand, C., Prouteau, A., Bouchard, R.H., Lipp, O., Lalonde, P., Nicole, L., Lesage, A., Stip, E., 2005. CANTAB explicit memory is less impaired in addicted schizophrenia patients. *Brain Cogn.* 59, 38–42.
- Ramirez, B.G., Blazquez, C., Gomez del Pulgar, T., Guzman, M., de Ceballos, M.L., 2005. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *J. Neurosci.* 25, 1904–1913.
- Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA* 264, 2511–2518.
- Ries, R.K., Russo, J., Wingerson, D., Snowden, M., Comtois, K.A., Srebnik, D., Roy-Byrne, P., 2000. Shorter hospital stays and more rapid improvement among patients with schizophrenia and substance disorders. *Psychiatr. Serv.* 51, 210–215.
- Ritzler, B.A., Strauss, J.S., Vanord, A., Kokes, R.F., 1977. Prognostic implications of various drinking patterns on psychiatric patients. *Am. J. Psychiatry* 134, 546–549.
- Salyers, M.P., Mueser, K.T., 2001. Social functioning, psychopathology, and medication side effects in relation to substance use and abuse in schizophrenia. *Schizophr. Res.* 48, 109–123.
- Sanguineti, V.R., Samuel, S.E., 1993. Comorbid substance abuse and recovery from acute psychiatric relapse. *Hospital and Community Psychiatry* 44, 1073–1076.
- Scheurich, A., 2005. Neuropsychological functioning and alcohol dependence. *Curr. Opin. Psychiatry* 18, 319–323.
- Serper, M.R., Bergman, A., Copersino, M.L., Chou, J.C.Y., Richarme, D., Cancro, R., 2000a. Learning and memory impairment in cocaine-dependent and comorbid schizophrenic patients. *Psychiatry Res.* 93, 21–32.
- Serper, M.R., Copersino, M.L., Richarme, D., Vadhan, N., Cancro, R., 2000b. Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. *J. Subst. Abuse* 11, 205–213.
- Sevy, S., Kay, S.R., Opler, L., van praag, H.M., 1990. Significance of cocaine history in schizophrenia. *J. Nerv. Ment. Dis.* 178, 642–648.
- Sevy, S., Robinson, D.G., Solloway, S., Alvir, J.M., Woerner, M.B., Bilder, R., Goldman, R., Lieberman, J., Kane, J., 2001. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. *Acta Psychiatr. Scand.* 104, 367–374.

- Silverstein, M.L., Mavrolefteros, G., Close, D., 2002. Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophr. Bull.* 28, 157–165.
- Smelson, D.A., Davis, C.W., Di Pano, R., Johnson, V., Losonczy, M.F., Ziedonis, D., 2002. Executive and motor skill functioning among cocaine-dependent schizophrenics. *J. Nerv. Ment. Dis.* 190, 200–202.
- Smelson, D.A., Davis, C.W., Eisenstein, N., Engelhart, C., Williams, J., Losonczy, M.F., Ziedonis, D., 2003. Cognitive disparity in schizophrenics with and without cocaine dependency. *J. Subst. Abuse Treat.* 24, 75–79.
- Stirling, J., Lewis, S., Hopkins, R., White, C., 2005. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophr. Res.* 75, 135–137.
- Swofford, C.D., Scheller-Gilkey, G., Miller, A.H., Woolwine, B., Mance, R., 2000. Double jeopardy: schizophrenia and substance use. *Am. J. Drug Alcohol Abuse* 26, 343–353.
- Thoma, R.J., Hanlon, F.M., Miller, G.A., Huang, M., Weisend, M.P., Sanchez, F.P., Waldorf, A.V., Jones, A., Smith, A., Formoso, M.J., Canive, J.M., 2006. Neuropsychological and sensory gating deficits related to remote alcohol abuse history in schizophrenia. *J. Int. Neuropsychol. Soc.* 12, 34–44.
- Tsuang, M.T., Simpson, J.C., Zronfonl, Z., 1982. Subtypes of drug abuse with psychosis. Demographic characteristics, clinical features, and family history. *Arch. Gen. Psychiatry* 38, 141–147.
- Zisook, S., Heaton, R., Moranville, J., Kuck, J., Jernigan, T., Braff, D., 1992. Past substance abuse and clinical course of schizophrenia. *Am. J. Psychiatry* 149, 552–553.