Neuropsychological frontal impairments and negative symptoms in schizophrenia

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Abstract

Negative symptoms have been associated to frontal lobe dysfunction in schizophrenia. However, neuropsychological studies that evaluated the correlation between performance in sensitive tests to the dorsolateral prefrontal cortex (DLPFC) and negative symptoms showed controversial results. During the last years, growing evidence has appeared that, not only the DLPFC but other prefrontal regions could be involved in schizophrenia. We evaluated schizophrenic patients and healthy controls using three "frontal tests": Wisconsin Card Sorting Test (WCST), Iowa Gambling Task (GT) and a Theory of Mind test (Faux Pas), and studied the relationship between performance in these tests and negative symptomatology. Schizophrenic patients had worse performance than normal controls in WCST, GT and Faux Pas test. The severity of the negative symptoms showed a moderate to high correlation with performance in the Faux Pas test. Our findings support the idea that different prefrontal regions could be affected in people with schizophrenia and that the damage of each of these regions could be, at least in part, independent of the damage of the others. Some negative symptoms could be associated to frontal medial cortex dysfunction.
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1. Introduction

Negative symptoms are the clinical features that best define schizophrenia; these are more stable, persistent and better predictors of long-term outcome than positive symptoms (McGlashan and Fenton, 1992). The similarity of negative symptoms with those clinical features that characterized frontal lobe damage led to the hypothesis that frontal lobe could be involved in the pathophysiology of schizophrenia. The hypothesis was reinforced by findings of Weinberger et al. (1986) who showed that patients with schizophrenia had less frontal lobe activation during a prefrontal type task. Moreover, different factorial models of schizophrenic symptoms associated negative symptoms with cognitive functioning. Crow (1980) reported that schizophrenic patients who had predominantly negative symptoms showed more cognitive impairments than those individuals with schizophrenia with predominantly positive symptoms.

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Liddle (1987) made a three-dimensional model that included a psychomotor poverty syndrome (essentially negative symptoms), a disorganization syndrome, and a reality distortion syndrome; and considered that the psychomotor poverty syndrome was associated with dorsolateral prefrontal cortex (DLPFC) impairments. In addition, further evidence about the association between negative symptoms and frontal lobe impairments come from structural and functional neuroimaging studies (Wolkin et al., 1992, 2003; Sanfilipo et al., 2000).

From the neuropsychological point of view, many authors demonstrated the association between negative symptoms and low performance in tests which are, at least in part, sensitive to frontal functions such as attention, working memory and executive functions (Breier et al., 1990; Buchanan et al., 1997; Addington and Addington, 1998; Heydebrand et al., 2004). However, these results are controversial, because they explain just 10% to 15% of variance (Heydebrand et al., 2004), and other authors could not replicate them (Abruzzese et al., 1996; Daban et al., 2002). Moreover, longitudinal studies did not find association between remission in symptoms and cognitive frontal functioning (Hughes et al., 2002; Hill et al., 2004). Inconsistency of these data could be explained by different ways. Cognitive deficits, still related to negative symptoms, could be a different construct (Hughes et al., 2002). Other alternative explanation is that these differences could be due to methodological issues, as sample heterogeneity or lack of differentiation between primary and secondary negative symptoms. A third hypothesis is possible. The majority of the studies that were made used cognitive functions which depend on DLPFC such as attention, working memory and executive functions; and it could be that negative symptoms rely on other prefrontal regions.

During the last decade, sensitive tests to impairments in other prefrontal regions, as the Iowa Gambling Task and Theory of Mind tests, began to be employed in patients with schizophrenia. Bechara et al. (1994) developed an experimental paradigm, the Iowa Gambling Task (GT), intended to simulate real-life decision making processes that is believed to be associated with the orbitofrontal cortex (OFC) supported by lesion (Bechara et al., 1994, 2000) and neuroimaging studies (Rogers et al., 1999). Up to date, performance of subjects with schizophrenia in the GT was evaluated in four studies. Wilder et al. (1998) did not find differences regardless of normal controls, while Beninger et al. (2003) showed impairments in patients medicated with a typical antipsychotics but not in those medicated with typical antipsychotics. Studies by Ritter et al. (2004) and Shurman et al. (2005) showed that patients with schizophrenia had worse performance than normal controls, although they did not show typical pattern of OFC patients. Regardless of negative symptoms, Ritter et al. did not find association in performance in the GT, while Shurman et al. showed a negative correlation between earned money (one of the measures of GT) and negative symptoms.

On the other hand, the ability to infer mental state (beliefs, thoughts and intentions) of others has been conceptualized as a mentalizing ability or theory of mind (ToM). Functional neuroimaging studies and electromagnetic recordings in healthy subjects, demonstrated that medial frontal cortex plays a critical role in the attribution of mental state of others (Goel et al., 1995; Calarge et al., 2003; Ishii et al., 2004). Many works reported ToM deficits in people with schizophrenia (Corcoran et al., 1995; Corcoran and Frith, 1996; Sarfati et al., 1999; Pilowsky et al., 2000; Mazza et al., 2001; Greig et al., 2004; Kelemen et al., 2005). However, Brune (2003) did not find differences in ToM between disorganized schizophrenic patients and normal controls after correcting IQ, and suggested that it is not clear whether performance on ToM tasks is associated with a "purely" deficient ToM mechanism or, rather, reflects a dysfunction of other cognitive capacities such as verbal memory and general intelligence. Regarding negative symptoms, the study of Corcoran et al. showed that patients of negative, incoherent and paranoid groups were those of worst performance. Mazza et al. classified their sample according to the Liddle three-dimensional model, and found that patients belonging to the psychomotor poverty group had worse results than those belonging to the disorganization and reality distortion groups. A more recent study (Kelemen et al., 2005) also reported an association between a ToM task and PANSS negative symptoms. Contrarily, Brune (2003) did not find correlation between ToM and psychopathology evaluated by the total score of Brief Psychiatric Rating Scale.

Altogether, these data bring evidence that, apart from the damage of the DLPFC, other frontal regions such as OFC and medial frontal cortex could be affected in schizophrenia. However, the dysfunction of these regions, as well as its relationship with negative symptomatology is not clear yet. The aim of this study is to estimate performance in patients with schizophrenia in sensitive tests to different frontal regions and determinate its grade of correlation with negative symptoms.

2. Methods

Twenty-one subjects (42% female) were selected consecutively from the population of stable outpatients with schizophrenia of "Alvear Psychiatric Hospital"

between June and December of 2004. Inclusion criteria were: 1) age between 18 and 55 years; 2) diagnosis of schizophrenia according DSM-IV by Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996); 3) psychiatrically stable (without changes either in medication or in psychiatric inpatient admission) during the last 4 months. Exclusion criteria were: 1) presence of other diagnosis in axis I of DSM-IV; 2) antecedent history of substance abuse; 3) history of mental retardation or neurological disease; 4) patients who were taken anticholinergics, antidepressants, mood stabilizers, or benzodiazepines in higher doses than 1 mg/day of clonazepam. Additionally, 15 healthy controls (60% female) matched by age and years of education were included: these had not antecedence of substance use disorder, or neurological or psychiatric disorder, or familiar history of schizophrenia, and they were not taken psychotropic medication. Controls were employers from Alvear Psychiatric Hospital and they were from similar socioeconomic background to patients. The study was approved by the Ethics Committee of Alvear Hospital and all subjects gave written informed consent for their participation after receiving a complete description of the study.

Patients with schizophrenia were evaluated with the SCID and the Positive and Negative Syndrome Scale (PANSS) (Kay and Opler, 1987); all subjects were evaluated with the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) and the Beck Depression Inventory (Beck et al., 1961).

2.1. Neuropsychological assessment

2.1.1. Intelligence quotient (IQ)

Current estimated IQ was measured in all subjects by Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). This consists of four subtests: similarities, vocabulary, block design and matrix; the first and the second one give a value of Verbal IQ and the others give the Performance IQ. A combined measure of four subtests allows obtaining a Full-Scale IQ.

2.1.2. Verbal memory

We used the Memory Battery of Signoret (Signoret and Whiteley, 1979). This test evaluates serial learning of a 12-word list of different semantic categories (3 trials), free delay recall, and recognition with semantic clues and multiple options.

2.1.3. Wisconsin Card Sorting Test (WCST) (Heaton, 1981)

This task is considered a somewhat more specific measure of DLPFC. It requires that the subject sorts response cards until they have matched 6 categories or sorted all 128 cards. Cards are matched based on color, shape and number and, with each sort, the subject receives a feedback (i.e. "right" or "wrong"). The rules with the cards are matched changes after 10 consecutive correct card sorts. We used as performance measures the number of categories, and the number of total and perseverative errors.

2.1.4. Iowa Gambling Task (Bechara et al., 1994)

In this test, subjects choose one of four decks (A, B, C, D; 60 cards for each deck) until 100 selections. After each selection, the participant gets a play money reward and/or penalty. Decks A and B have high rewards and penalties while decks C and D have low rewards and penalties. Additionally, decks A and C have high frequency of penalties and decks B and D low. A greater selection of decks A and B (disadvantaged decks) could result in a net loss and a greater selection of decks C and D (advantage decks) could result in a net gain. Typically, OFC patients take higher risks (A+B>C+D), choose more disadvantaged decks over all test and earn less money compared with normal controls (Bechara et al., 1994, 2000). We used as performance measures number of cards chosen from each deck (A, B, C, or D), total advantaged minus disadvantaged decks, amount of money earned, and chronological selection of advantageous versus disadvantageous decks, in 5 blocks of 20 cards.

2.1.5. "Faux Pas" test (Stone et al., 1998)

This ToM test consists of 10 histories (translated from its original version to Spanish language) in which one of the characters says something that it would be better not to say. After reading the history aloud, the interviewer asks: (1) 'Does somebody say something that it would be better not to say?'; in case of an affirmative answer, (2) 'Who?' and (3) 'Why do you think he/she says so?'. Although the answer to question (1) is affirmative or negative, the interviewer makes a reality question to test general comprehension and memory. One point is given for each correct answer and none for the incorrect ones. Alternatively with these histories, ten control histories are read in which there are no problems, and the first and reality questions are asked (one point for correct answer and none for incorrect one). Once 20 histories have been read, a ToM index (IToM) can be calculated as follows: somebody+who+why+control histories/40 (total score ranges from 0 to 1). By the same manner, a memory index can be obtained: reality question Faux Pas+reality question control history/20 (total score ranges from 0 to 1).

t1.1   Table 1
       Clinical and demographical characteristics of the participants [values
t1.2   are expressed as mean (S.D.)]

Variable	Schizophrenic patients	Normal controls	Test ($df=34$)	
Age	32.66 (8.96)	34.96 (10.93)	$t=0.67$	t1.4
Years of education	10.42 (2.15)	10.6 (1.84)	$t=0.7$	t1.5
Beck Depression Inventory	6.33 (2.85)	6.13 (3.18)	$t=0.19$	t1.6
SANS	52.19 (13.18)	3.13 (2.61)	$t=13.21*$	t1.7
PANSS positive	10.76 (3.19)	–	–	t1.8
IQ level				t1.9
Full-scale	94 (12.95)	99.06 (9.45)	$t=1.35$	t1.10
Verbal	100.42 (13.51)	101.33 (9.28)	$t=0.24$	t1.11
Performance	88.61 (11.65)	94 (10.18)	$t=1.47$	t1.12

SANS: Schedule for the Assessment of Negative Symptoms; PANSS:
t1.13 Positive and Negative Syndrome Scale; IQ: intelligence quotient.
t1.14   * $P<0.001$.

243   One physician (D.M.), examined all subjects on both
244 clinical and neuropsychological examination according
245 to a standardized order. The total procedure was done in
246 2 interviews of 90 min each in the term of a week.

247 *2.2. Data analysis*

248   The Statistical Package for the Social Science (SPSS)
249 version 9 for Windows was used for all statistical
250 analysis (SPSS, 1999). Independent sample *t*-test was
251 employed for between-group comparison on continuous
252 variables (age, years of education, SANS score, Beck
253 score, and performance in WCST, GT, and Faux Pas
254 test). In the case of verbal memory measures (nonpara-
255 metric variables), results were confirmed by the
256 Kolgomorov–Smirnov test. Analysis of covariance
257 (ANCOVA) was used to compare the performance of
258 patients and controls in Faux Pas test, with total IQ,
259 serial learning, and free delay recall as covariates. Group
260 differences in the chronological selection of advanta-
261 geous versus disadvantageous decks were examined
262 using a 2 (group)×5 (blocks of 20 cards) repeated-
263 measures ANOVA. Pearson correlation coefficients
264 were calculated to asses the relationship between
265 clinical measures (length of illness, SANS score and
266 PANSS positive score) and performance on WCST, GT,
267 and Faux Pas test. All significance was established at
268 0.05.

269 **3. Results**

270   Clinical and demographical variables are shown in
271 Table 1. Groups did not differ in age, educational level
272 and current IQ. In the schizophrenic group, the mean

273 age at illness onset was 23.8 years (5.5 years), and the
274 mean length of illness was 8.57 years (6.36 years). All
275 patients were taken antipsychotic medication at the
276 moment of evaluation: 11 clozapine (290.9±117.9
277 mg/day), 6 risperidone (2.9±0.2 mg/day), and 2 halo-
278 peridol (2.75±0.35 mg/day). Additionally, 6 patients
279 were taken clonazepam (0.6±0.3 mg/day). As we
280 expected, subjects with schizophrenia had greater
281 values of negative symptoms in the SANS than normal
282 controls. There was no difference between groups in
283 depressive symptomatology.

284   Results of neuropsychological evaluation are shown
285 in Table 2. Patients with schizophrenia did more total
286 errors ($t=2.8$, $P=0.008$) and perseverative errors
287 ($t=2.94$, $P=0.005$) in WCST. There was no association
288 between these WCST measures and length of illness,
289 PANSS positive subscale, SANS total score or the serial
290 learning and free delay recall. However, when each
291 SANS subscale was evaluated, the attention one
292 correlated significantly with the number of categories

Table 2   t2.1
Neuropsychological evaluation of both groups [values are expressed as
mean (S.D.)]   t2.2

	Schizophrenic patients	Normal controls	Test ($df=34$)	
Verbal memory				t2.4
Serial learning	7.85 (1.82)	9.6 (1.24)	$KS=1.24$	t2.5
Free delay recall	5.85 (2.41)	8.13 (1.64)	$KS=1.24$	t2.6
Recognition	11.09 (1.22)	11.73 (0.45)	$t=7.35$	t2.7
Wisconsin Card Sorting Test				t2.8
Categories	4.09 (1.99)	5.53 (0.83)	$KS=1.21$	t2.9
Total errors	41.66 (19.6)	26.33 (13.16)	$t=2.8**$	t2.10
Perseverative errors	22.47 (12.06)	12 (7.79)	$t=2.94**$	t2.11
Iowa Gambling Task				t2.12
No. cards chosen from deck A	20.09 (6.62)	15.2 (3.74)	$t=2.57*$	t2.13
No. cards chosen from deck B	30 (10.7)	26.66 (10.46)	$t=0.93$	t2.14
No. cards chosen from deck C	23.85 (10.93)	21.13 (9.25)	$t=0.8$	t2.15
No. cards chosen from deck D	26.04 (9.57)	37 (8.75)	$t=3.56**$	t2.16
Advantaged − Disadvantaged decks	0.76 (28.03)	17.06 (24.87)	$t=1.38$	t2.17
Amount of money earned	954 (1578)	1631 (1013)	$t=1.45$	t2.18
Faux Pas				t2.19
Theory of mind index	0.82 (0.11)	0.94 (0.05)	$t=3.93***$	t2.20
Memory index	0.89 (0.09)	0.91 (0.05)	$t=0.77$	t2.21

   * $P<0.05$.   t2.22
  ** $P<0.01$.   t2.23
 *** $P<0.001$.   t2.24

293 ($r=-0.44$; $P=0.04$), total errors ($r=0.46$; $P=0.03$) and
294 perseverative errors ($r=0.46$, $P=0.03$).
295   In the GT, there was only significant difference
296 between subjects with schizophrenia and normal con-
297 trols in deck A selection ($t=2.57$, $P=0.01$) and in deck D
298 selection ($t=3.56$, $P=0.001$) (Table 2). Regardless of
299 chronological selection of cards, there was significant
300 main effects for block ($F=11.21$, $P=0.001$), while
301 effects for group approached significance ($F=3.04$,
302 $P=0.09$) and interaction effect was not significant
303 ($F=1.36$, $P=0.25$) (Fig. 1). There was no association
304 between performance in GT and PANSS positive, SANS
305 or length of illness. There was no correlation with
306 different measures of GT and verbal memory.
307   Patients had worse performance than controls in Faux
308 Pas test ($t=3.93$, $P=0.0003$). We did not find differences
309 in both groups in memory index (Table 2). The
310 differences in IQ and verbal memory between the groups
311 were covaried out using an analysis of covariance and the
312 between group differences in Faux Pas test performance
313 remained significant ($F=6.16$; $P=0.01$). There was no
314 correlation between IToM and length of illness, PANSS
315 positive, verbal memory or with any of the WCST and
316 GT measures. We found a moderate to high negative
317 correlation between IToM and SANS total score ($r=$
318 -0.68; $P=0.0008$). The analysis of each SANS subscale
319 revealed a negative correlation between IToM and
320 emotional withdrawal ($r=-0.58$; $P=0.006$), alogia ($r=$
321 -0.6; $P=0.004$) and affective flattening ($r=-0.52$;
322 $P=0.01$).
323   Although this study was not primary designed to
324 evaluate the antipsychotic effect over negative symp-
325 toms and cognition, we did an analysis dividing patients
326 in two groups: those who were medicated with clozapina
327 ($n=11$) and those medicated with other antipsychotics

Fig. 1. Decision making over the time.

328 ($n=10$). There was no difference in any of the clinical
329 and neuropsychological measures.

4. Discussion

331   The aim of this paper was to study frontal lobe
332 functioning in a group of schizophrenic patients with
333 sensitive tests to DLPFC (WCST), OFC (GT) and
334 medial frontal cortex (ToM). According to the DLPFC
335 impairments extensively reported in literature (Wein-
336 berger et al., 1986; Callicot et al., 2003), our sample of
337 patients with schizophrenia had more total and persev-
338 erative errors than normal controls in WCST.
339   Regardless of GT, patients with schizophrenia chose
340 more than controls deck A (disadvantageous deck) and
341 less than controls deck D (advantageous deck).
342 However, we did not find significant differences
343 between both groups in other measures of GT. This
344 could be because of a type II error, since there were
345 some measures, such as advantageous minus disadvan-
346 tageous cards and effects for group in chronological
347 selection of cards, that were almost significant ($P=0.07$
348 and 0.09, respectively).
349   Subjects with schizophrenia had worse performance
350 in Faux Pas test, and this difference remained significant
351 after controlling IQ total score, serial learning and free
352 delay recall. These results support data from previous
353 studies that reported ToM deficits in schizophrenic
354 patients (Corcoran et al., 1995; Sarfati et al., 1999;
355 Mazza et al., 2001). ToM impairments in our stable
356 outpatient sample, with low levels of positive and
357 depressive symptoms, could be considered a trait marker
358 more than a state marker. What is more, Janssen et al.
359 (2003) showed ToM deficits in no psychotic relatives of
360 schizophrenic subjects.
361   Taken together, these data support that, apart from
362 DLPFC, other frontal regions such as OFC and frontal
363 medial cortex (or their subcortical connections) are
364 involved in schizophrenia. Further evidence of the OFC
365 and frontal medial cortex damage comes from neuro-
366 pathological and neuroimaging studies (Convit et al.,
367 2001; Wolkin et al., 2003; Memhet Haznedar et al.,
368 2004). Dysfunction of different prefrontal regions could
369 be, at least in part, independent from the dysfunction of
370 other regions, because of the lack of correlation between
371 all WCST, GT and ToM task measures. In other words,
372 subjects with schizophrenia could have more or less
373 grade of dysfunction of different prefrontal regions.
374   Taking into account the controversial relationship
375 between negative symptoms and frontal function men-
376 tioned above, the second aim of this study was to corre-
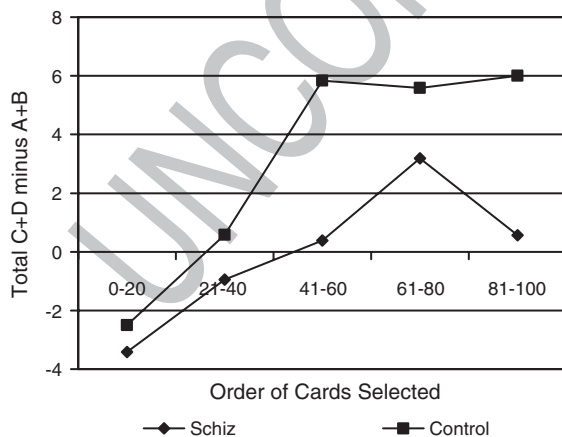377 late negative symptomatology with neuropsychological

measures. We did not find association between SANS total score and any of the WCST measures. However, a posterior analysis of each SANS subscale revealed a significant correlation between the attention subscale and the three WCST measures. This could not be surprising, considering that both attention and executive functions depend on, at least in part, the DLPFC integrity (Fuster, 1997).

Similarly to Ritter et al. (2004) and different from Shurman et al. (2005), we did not find association between negative symptoms and GT performance.

Our results showed a moderate to high correlation between negative symptomatology and mentalizing ability, that is particularly true for alogia, affective flattening and anhedonia. Previous research that used categorical measures of negative symptoms, reported an association between patients with negative symptoms and deficits in ToM tasks (Corcoran et al., 1995; Mazza et al., 2001). The nature of this association is not clear yet; Mazza et al. proposed that ToM impairments in people with schizophrenia with predominance of negative symptoms could be a selective cognitive deficit. An alternative explanation could be that both ToM impairments and some negative symptoms could depend on frontal medial cortex or its subcortical connections. As we have already mentioned, there is strong evidence that frontal medial cortex plays a critical role in mentalizing ability, in healthy and schizophrenic subjects (Russell et al., 2000; Brunet et al., 2003; Calarge et al., 2003; Abdi and Sharma, 2004). Indirect evidence that some of the negative symptoms could be due to frontal medial cortex dysfunction comes from other clinical populations. First, people with high functioning autism and Asperger's syndrome, who have clear deficiencies in ToM tasks secondary to frontal medial cortex hypoactivity (Happe et al., 1996), have similar clinical features to negative symptoms in schizophrenia. In the same manner, it has been reported autism symptoms that co-vary with negative symptoms in people with schizophrenia (Sheitman et al., 2004). Second, there is a strong relationship between negative symptoms and the concept of apathy defined by Marin (1990). Apathy has been related to anterior cingulate region hypoactivity in patients with dementia of Alzheimer's type and organic personality disorders (Migneco et al., 2001). Likewise, Fuster (1997) proposed, in his description of prefrontal syndromes, that apathy is prominent in frontal medial lesions and it is not in those of the DLPFC and OFC. Until now, just two papers studied the clinical construct of apathy in people with schizophrenia. Kiang et al. (2003) found correlation between apathy and emotional withdrawal, while in the study of Roth et al. (2004), only schizophrenic patients with high levels of apathy had a bilateral reduction of frontal lobe volume. In spite of these indirect evidences, the possible relationship between some negative symptoms and frontal medial cortex damages results are speculative nowadays. Future works with functional neuroimages could contribute to clarify it.

Some limitations of our study should be taken into account. The small size of the sample could have affected our statistical power, particularly regardless of GT measures. Second, negative symptoms measured with SANS do not allow differentiation between primary and secondary negative symptoms. This is a limitation of almost all studies about neuropsychology of schizophrenia. We consider that distinction between primary and secondary negative symptoms is important because it could be possible that cognitive impairments have a stronger association with primary than with secondary negative symptoms. However, as patients of our study had low levels of positive and depressive symptoms and have taken relatively low doses of medication, it could be possible considering that negative symptoms were predominantly primary. Finally, our design was not blind in clinical and neuropsychological evaluation results.

In summary, our results show that different prefrontal regions can be affected in schizophrenia, and that the dysfunction of each one could be, at least in part, independent from the others. Additionally, we reported a correlation between some negative symptoms and low performance in a ToM test that is sensitive to frontal medial cortex dysfunction. The association between negative symptoms and frontal medial cortex dysfunction is not clear yet, and further studies are necessary to lighten it.

5. Uncited reference

Sharma and Harvey, 2000

Acknowledgments

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