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Statistical differentiation between direct and indirect effects of neuroleptics on negative symptoms

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Abstract The differentiation between primary and secondary negative symptoms in schizophrenia (Carpenter et al. 1985) is an important issue. Path analysis allows to estimate statistically whether, and in which degree, the effect of a neuroleptic on negative symptoms is mediated by effects on positive, extrapyramidal, and depressive symptoms (Möller et al. 1995). If certain causal relationships are theoretically assumed – as proposed by Carpenter et al. (1985) – then path analysis can be applied to estimate the quantitative degree of these relationships, although the causal directions cannot be inferred from path analysis itself. Especially it can be estimated whether there is sufficient evidence for a "direct effect" of neuroleptic treatment on (primary) negative symptoms, an effect which is not mediated by positive, extrapyramidal, and/or depressive symptoms. We show the correspondence between the applied path model and several simple regression equations which can be estimated with standard statistical software. Moreover, we report some Monte Carlo studies showing that the results reported by Möller et al. (1995) – a "direct effect" of risperidone (6 mg) on negative symptoms compared with haloperidol (20 mg) – cannot be explained by a path model in which, everything else being equal, positive symptoms depend on negative symptoms instead of the other way around.

Key words Schizophrenia · Negative symptoms · Path analysis · Neuroleptics · Risperidone

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Introduction

Carpenter et al. (1985) introduced the important distinction between primary and secondary negative symptoms. In contrast to primary negative symptom patterns, secondary negative symptom patterns are caused by positive symptoms, side effects of neuroleptics (especially extrapyramidal symptoms), depression, or a lack of social stimulation. It is still unclear to what degree various neuroleptics reduce primary and/or secondary negative symptoms; this is partly due to methodological problems (Möller 1993). Möller et al. (1995) devised a path analytical model for the estimation of direct and indirect (secondary) treatment effects on negative symptoms of schizophrenia (cf. also Müller and Möller 1994). Partial reanalysis of the North American risperidone trial (cf. Marder and Meibach 1994) led Möller et al. (1995) to conclude that the significant superiority of risperidone (6 mg) to haloperidol (20 mg) in reducing negative symptoms on the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) cannot be explained simply by its greater effect on positive or extrapyramidal symptoms, i.e., secondary symptoms. Figure 1 shows the relevant path model with the estimated coefficients, all of which are significant ($p < 0.05$).

In Fig. 1 positive symptoms were also recorded using the PANSS, and extrapyramidal symptoms with the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al. 1980). In the analyses carried out by Möller et al. (1995), depressive symptoms showed very little correlation with negative symptoms; thus, they were left out of the suggested path model. Hospitalization effects were not taken into account because the necessary data were not available. The present study elaborates on and evaluates the suggested path model from a methodological standpoint in order to better assess the applicability of this approach for the problems posed by secondary negative symptoms.

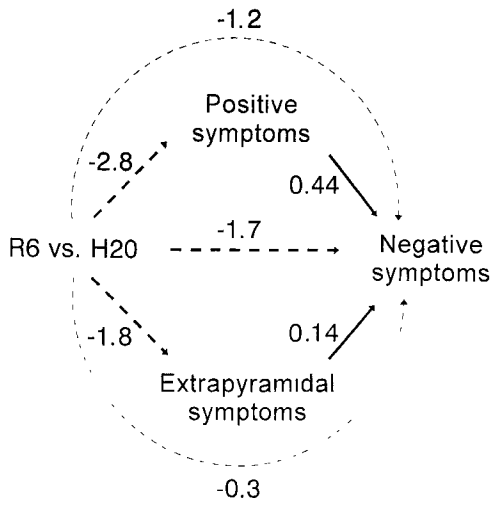

Fig. 1 Path model estimates of direct and indirect effects of treatment with risperidone (6 mg) vs haloperidol (20 mg) on negative symptoms of schizophrenia. (From Muller and Moller 1994)

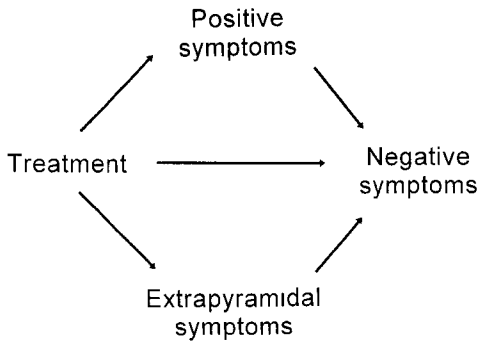

Fig. 2 Path model of direct and indirect effects of treatment with risperidone (6 mg) vs haloperidol (20 mg) on negative symptoms of schizophrenia. (From Müller and Möller 1994)

Theoretical assumptions and empirical evidence in the path model

To understand the results obtained by Möller et al. (1995), it is important to draw a distinction between the theoretical assumptions made in the model and, in contrast, the empirical results of the data analysis. Figure 2 shows the assumptions made by Möller et al. (1995) in the form of a path model.

Perhaps the most important point to make about Fig. 2 is that it represents theoretical considerations. Thus, the causal connections between the variables are not drawn from empirical data, but instead, are postulated. However, there is no question of a new or particularly daring speculation on the connection between the variables presented, but rather a depiction of the consensus view of the problems posed by primary and secondary negative symptoms (cf. Carpenter et al. 1985): At least some of the negative symptoms observed can be understood as a reaction to productive symptoms, just as others are actually an effect of extrapyramidal symptoms. The principal thesis of this article and of Möller et al. (1995) is that it is possible statistically to estimate direct and indirect effects of a treatment taking the causal connections depicted in Fig. 2 into account. In other words, if we accept a causal structure as shown in Fig. 2 (theoretical assumption), we can estimate statistically the degree of the postulated connections (empirical result). In particular, therefore, we can judge empirically whether a treatment has a direct effect on the negative symptoms if we assume that the effects of treatment on positive and extrapyramidal symptoms also act indirectly on negative symptoms. Figure 2 contains "only" pathways for productive and extrapyramidal symptoms, because, according to current experience, risperidone (6 mg) is distinguished from haloperidol (20 mg) specifically by its more effective action on productive and extrapyramidal symptoms (Marder and Meibach 1994). Another reason not to include depressive symptoms in the analysis is that preliminary analyses carried out by Möller et al. (1995) did not show any statistically significant relationship between improvement in depressive symptoms and improvement in negative symptoms. The causes of secondary negative symptoms cited by Carpenter et al. (1985) are all given in Fig. 2, with the exception of hospitalization effects, which could not be checked on the basis of the available data.

Statistical estimation

Statistical estimation of the effects postulated in Fig. 2 requires further assumptions. The first of these is that the relationship between negative symptoms and positive or extrapyramidal symptoms is linear. This assumption is made for pragmatic reasons and is understood to be an approximation made for lack of a better, alternative hypothesis. Interactive effects are not included in Fig. 2, and thus no account is taken of them statistically. Because our principal interest is the changes resulting from treatment, the differences between baseline and final observation values were analyzed as dependent variables. In addition, the dependence of these differences on the baseline values was included in the calculations. These assumptions can be expressed as the following three regression equations:

$$\text{Pos (e–b)} = k_1 + a_1 * \text{Pos (b)} + d_1 * T \quad (1)$$

$$\text{ESRS (e–b)} = k_2 + a_2 * \text{ESRS (b)} + d_2 * T \quad (2)$$

$$\text{Neg (e–b)} = k_3 + a_3 * \text{Neg (b)} + b_3 * \text{Pos (e–b)} + c_3 * \text{ESRS (e–b)} + d_3 * T \quad (3)$$

where, Pos (e–b) is the difference in positive scores between the final observation (end point) and the baseline; Pos (b) is the baseline score of the PANSS positive scale; ESRS is the overall ESRS score (overall medical rating of parkinsonism, dystonia, and dyskinesia), and Neg is the score on the PANSS negative scale; T represents a dummy variable, which has the value 0 for the haloperidol group and the value 1 for the risperidone group; the parameters with subscripts, k_1 to d_3, must be estimated empirically.

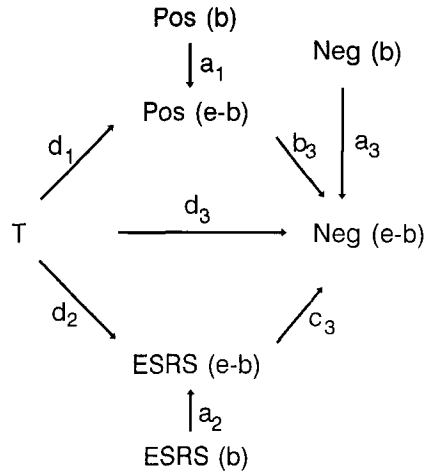

Fig. 3 Path model showing all the parameters to be estimated [cf Eqs. (1)–(3) in text]

Figure 3 shows the path model with all parameters to be estimated.

A path-analysis program, such as LISREL (Jöreskog and Sörbom 1988) could approximately assess this model. However, because our model postulates relationships between directly observable variables, the three equations cited may also be calculated by three separate regression analyses which correspond exactly to Eqs. (1)–(3). A path analysis with LISREL would yield different results only if the model contained latent variables, which are estimated from several observable variables. Tables 1–3 show the results of the three regression analyses corresponding to Eqs. (1)–(3).

The path model shown in Fig. 1 represents the most important results in Tables 1–3.

Table 1 Results of regression analysis for Eq. (1) [Pos (e–b) = $k_1 + a_1$ * Pos (b) + d_1 * T; $R^2 = 0.22$; $p < 0.001$]

Parameter	Estimate	t for parameter = 0	p
k_1	2.2	1.30	0.196
a_1	–0.32	–5.02	< 0.001
d_1	–2.8	–2.70	0.007

Table 2 Results of regression analysis for Eq. (2) [ESRS (e–b) = $k_2 + a_2$ * ESRS (b) + d_2 * T; $R^2 = 0.21$; $p < 0.001$]

Parameter	Estimate	t for parameter = 0	p
k_2	1.8	2.73	0.007
a_2	–0.33	–7.86	< 0.001
d_2	–1.8	–2.23	0.027

Table 3 Results of regression analysis for Eq. (3) [Neg (e–b) = $k_3 + a_3$ * Neg (b) + b_3 * Pos (e–b) + c_3 * ESRS (e–b) + d_3 * T; $R^2 = 0.41$; $p < 0.001$]

Parameter	Estimate	t for parameter = 0	p
k_3	8.2	5.06	< 0.001
a_3	–0.31	–5.10	< 0.001
b_3	0.44	7.76	< 0.001
c_3	0.14	2.02	0.045
d_3	–1.7	–2.07	0.040

Simulation results on the relevance of the model

Initially, some of our readers may doubt whether regression analyses actually enable adequate approximations of the pathways postulated in Fig. 3. We have therefore used a small simulation to establish this. Ten regression analyses were carried out, each using 100 sets of data generated from the following equations:

$$\text{Treatment} = \text{random (2)} \quad (4)$$

$$\text{Positive symptoms} = \text{random (7)} + 2.8 * \text{treatment} \quad (5)$$

$$\text{Negative symptoms} = \text{random (7)} + 1.7 * \text{treatment} + 0.44 * \text{positive symptoms} \quad (6)$$

in which random (2) is a random number equal to 0 or 1 and random (7) is a random number between 0 and 6.

Figure 4 shows the model simulating a small section of our empirical results from Fig. 1.

The question is whether the coefficients a and b in a regression analysis of the form "negative symptoms = k + a * treatment + b * positive symptoms" have actually been adequately estimated. Table 4 shows that the estimates of the 10 simulated data sets for 100 people, although admittedly not often reproducing the simulated parameters exactly, are scattered around the original parameters and, in particular, they correctly identify the simulated relationships as statistically significant.

The next question is whether a theoretical model, such as that in Fig. 5, could possibly lead to the same estimates.

The model in Fig. 5 was likewise run 10 times using 100 data sets, the equations now being:

$$\text{Treatment} = \text{random (2)} \quad (7)$$

$$\text{Positive symptoms} = \text{random (7)} + 2.8 * \text{treatment} + 0.44 * \text{negative symptoms} \quad (8)$$

$$\text{Negative symptoms} = \text{random (7)} + 1.7 * \text{treatment} \quad (9)$$

In the model in Fig. 5 positive and negative symptoms are again correlated, but the positive symptoms depend on the negative symptoms and not the other way around as in Fig. 4.

Table 5 shows the estimates for the "false" model "negative symptoms = k + a * treatment + b * positive

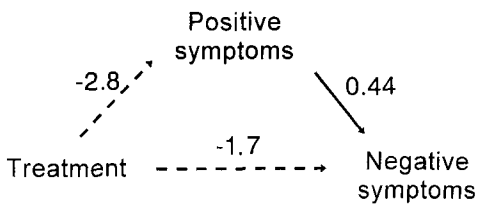

Fig. 4 The first path model simulated

Table 4 Results of ten simulations each using 100 simulated subjects and the following model: negative symptoms = random (7) – 1.7 * treatment + 0.44 * positive symptoms; positive symptoms = random (7) – 2.8 * treatment; path coefficients for Eq. (1). M parameter of the model

	M	Simulation[a]									
		1	2	3	4	5	6	7	8	9	10
a (treatment)	–1.7	–1.8	–1.2	–1.5	–2.0	–2.8	–2.0	–2.6	–2.2	–1.3	–1.1
b (positive symptoms)	0.44	0.39	0.25	0.55	0.36	0.43	0.38	0.39	0.39	0.46	0.48
R^2	0.41	0.42	0.23	0.49	0.41	0.55	0.49	0.50	0.45	0.36	0.34

[a] $p < 0.05$ for all simulation values

Table 5 Results of ten simulations each using 100 simulated subjects and the following model: negative symptoms = random (7) – 1.7 · treatment (+ 0 · positive symptoms); positive symptoms = random (7) – 2.8 · treatment + 0.44 · negative symptoms; path coefficients for Eq. (1). M parameter of the model

	M	Simulation[a]									
		1	2	3	4	5	6	7	8	9	10
a (treatment)	–1.7	–1.3	–1.4	–1.9	–1.6	–1.9	–1.8	–1.9	–1.6	–1.6	–2.0
b (positive symptoms)	0	0.07	0.05	–0.13	–0.05	0.12	–0.01	0.01	0.09	–0.03	–0.11
R^2		0.12	0.13	0.16	0.11	0.23	0.16	0.20	0.18	0.14	0.16

[a] $p < 0.05$ for all simulation values except for those for positive symptoms

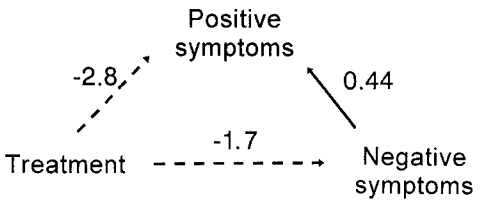

Fig. 5 The second path model simulated

symptoms." Table 5 shows correctly that in every case the parameter b was not significant, so that the model did not show that negative symptoms depended on positive symptoms when actually the positive symptoms depended on the negative symptoms. In LISREL nomenclature it would be said that the models in Figs. 4 and 5 are not equivalent, i.e., they do not imply the same covariance matrix. With regard to the appraisal of the model we used at the start (Fig. 1), this means that the assumed and confirmed effect of the reduction of positive symptoms on the reduction of negative symptoms does not necessarily imply the converse.

Conclusion

This study has expanded on a model for the assessment of direct and indirect effects on negative symptoms of schizophrenia suggested and used by Möller et al. (1995). In particular, the equivalence of the path model appraised with three regression equations has been described, and the results of the corresponding regression analyses have been presented in detail. Furthermore, a simulation study was used to prove that an estimate of direct and indirect treatment effects can be obtained with this approach, and even that the observed regression of the negative symptoms on the positive symptoms generally cannot be recreated by the reverse relationship.

However, although we think that the outlined approach to estimate the relationship between drug treatment, extrapyramidal symptoms, positive symptoms, and negative symptoms presents some progress, several problems should be kept in mind.

Because the dependent variables were differences between end-point scores and baseline scores of symptoms, and the baseline scores were also predictors, the R^2 in Tables 1–3 are biased (i.e., too large) by an unknown influence of mere chance. Therefore, caution is required in the interpretation of the R^2. Despite this problem, the proposed evaluation strategy makes sense from a substantial point of view. Differences between baseline and end-point scores are appropriate indicators of treatment effects, depend on baseline scores, and because of the problem with the interpretation of the resulting R^2, we refrained consequently from interpretation of these R^2. This is acceptable, because the precise amount of R^2 is of secondary interest in this context.

Other reservations relate to the question of whether the proposed model is completely appropriate. The reported estimations are only correct if (a) there are no relevant variables omitted in the model, (b) there are no non-linear relationships between shift in positive symptoms or shift in extrapyramidal symptoms, and shift in negative symptoms, and (c) there are no interactions between the predictors of shift in negative symptoms. These are the usual reservations when a linear model is estimated. We did

some unpublished analyses to check whether reservations (b) and (c) might be problematic with our data. There was no hint in this direction. Thus, reservation (a) seems more problematic. Although some orienting analyses showed that shift in negative symptoms seemed not to be related to shift in depressive symptoms, this is clearly contrary to the assumptions of Carpenter et al. (1995) and our own expectations. Moreover, there may be important variables influencing shift in negative symptoms which were not assessed in the study which we reanalyzed. In summary, we are aware that the proposed model may finally prove to be too simple. However, we think that it is an acceptable approximation and a good starting point with the available knowledge and empirical data.

Finally, the most important point is the interpretation of our results. The reported direct effect of risperidone on negative symptoms is defined by the model and has no established relevance to clinical therapeutic effects. A clear answer to the question of whether treatment-resistant chronic negative symptoms are successfully treated by a certain compound requires another study design and patient selection than was given as the basis of our reanalyses. Thus, our a posteriori statistical analyses are only able to provide preliminary evidence for direct drug effects of risperidone on negative symptoms. Therefore, final conclusions on this topic cannot yet be drawn, but require further investigations.

References

Carpenter WT Jr, Heinrichs DW, Alphs LD (1985) Treatment of negative symptoms. Schizophr Bull 11 (3): 440–452

Chouinard G, Ross-Chouinard A, Annable L, Jones BG (1980) The Extrapyramidal Symptom Rating Scale (ESRS). Can J Neurol Sci 7: 233

Jöreskog K, Sörbom D (1988) LISREL 7. SPSS Inc, Chicago, Ill

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13 (2): 261–276

Marder SR, Meibach RC (1994) Risperidone in the treatment of schizophrenia. Am J Psychiatry 13: 25–40

Möller H-J (1993) Neuroleptic treatment of negative symptoms in schizophrenic patients. Efficacy problems and methodological difficulties. Eur Neuropsychopharmacol 3: 1–11

Möller H-J, Müller H, Chouinard G, Borison RL, Schooler NR (1995) A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. Eur Arch Psychiatry Clin Neurosci 245: 45–49

Müller H, Möller H-J (1994) Methodische Probleme bei der Analyse von Neuroleptikaeffekten auf Negativsymptomatik. In: Moller H-J, Laux G (eds) Fortschritte in der Diagnostik und Therapie schizophrener Minussymptomatik. Springer, Berlin Heidelberg New York, pp 63–77