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# Acute psychopathology as a predictor of global functioning in patients with ICD-10 non-affective psychosis: A prospective study in 11 European countries

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ABSTRACT

This prospective analysis aimed to study the influence of psychopathological dimensions on the global functioning of persons suffering from psychotic disorders, taking into account the role of a broad range of potential confounders. A large international cohort (n = 1888) with ICD-10 non-affective psychosis was evaluated both at baseline during a hospital admission and three months after discharge. Trained interviewers administered a global functioning scale (GAF) and a psychopathological scale (BPRS) at baseline and follow-up). Baseline BPRS psychopathological dimensions were extracted using Principal Component Analysis. Results of multiple linear regression analyses demonstrated that affective symptoms (depressive or manic) prospectively predict a better global functioning, whilst agitation/cognitive symptoms determined poorer global functioning. Other predictors showing an independent effect on better global functioning were medication compliance, country of residence, female gender, married or coupled status, younger age and having a diagnosis of schizoaffective disorder rather than schizophrenia or other ICD-10 psychosis. A predicting model for global functioning in patients with psychosis is provided, showing that assessment of affective and agitation/cognitive symptoms should be emphasised during admission as they can be more informative than positive/negative symptoms in prospectively planning follow-up care that is geared towards a better functional recovery.



## 1. Introduction

Psychotic disorders may have devastating consequences and lead to severe deterioration of sufferers' global functioning (Thaker and Carpenter, 2001), as persons suffering from psychotic disorders generally experience a dysfunction in activities of daily living (ADL) such as work, education, interpersonal and family relationships, communication abilities and self-care (Patterson et al., 1998; Wiersma et al., 2000; Sharma and Antonova, 2003; Thornicroft, et al., 2004). Indeed, an assessment of the patient's global functioning was added in the Diagnostic and Statistical Manual for Mental Disorders 4th edition (DSM-IV) (American Psychiatric Association, 1994), constituting the Axis V of a comprehensive diagnosis, and a degree of global functioning loss is also required for the diagnosis of schizophrenia in the International Classification of Diseases, 10th Edition (ICD-10) (WHO, 1992).

Global functioning can be reliably assessed using validated instruments, such as the Global Assessment of Functioning (GAF) (Goldman et al., 1992). Psychometric properties of GAF have often been criticised in the literature (Moos et al., 2002; Vatnaland et al., 2007). Hence, some authors have suggested that its validity needs

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further exploration as it includes, not only functional components, but also mental symptoms (Aas, 2010). Nonetheless, the GAF can be considered the most widely used instrument for functioning assessment both in clinical and research practise.

### 1.1. Factors related to global functioning

Amongst people with psychotic disorders (Vázquez-Barquero et al., 1999; Usall et al., 2002; Haro et al., 2008) or those who are at a high risk for psychotic disorders (Willwhite et al., 2008), women seem to have a better level of global functioning than men. Similarly, younger age (Zipursky and Schulz, 2002; Wittorf, et al., 2008) and being under psychological and pharmacological treatment (Miyamoto et al., 2003; Valencia et al., 2004) have also been reported as associated with better global functioning. Cognitive impairment has also been consistently associated with poorer global functioning (Green et al., 2004) or some of its components, such as social and everyday dysfunctioning (Smith et al., 1999; Green et al., 2000; Green, 2006; Harvey et al., 2009), self care abandonment (Harvey et al., 1998) or social skills deficits (Palmer et al., 2002) in persons suffering from psychotic disorders. There is some debate as to whether the influence of cognitive impairment on global functioning is mediated by other psychopathology (e.g. negative symptoms) (Kurtz, 2006; Ventura et al., 2009) or whether psychopathology and cognitive impairment exert an independent effect on global functioning (Rocca et al., 2009; Shamsi et al., 2011). Villalta-Gil et al. (2006), in their study including patients suffering from schizophrenia, found that negative symptomatology constituted the psychopathological factor that explained the major part of total disability in patients with schizophrenia.

### 1.2. Psychopathology and global functioning

There is evidence that psychopathological symptoms, nonetheless, play a major role in global functioning of patients suffering from a psychotic disorder. Thus, the presence of more negative symptoms was consistently found to be associated with impairment of global functioning in cross sectional studies (Addington and Addington, 1999; Hofer et al., 2006; Rocca et al., 2009) or to be prospective predictors of global functioning (Lindstrom, 1996; Herbener and Harrow, 2004; Kurtz, 2006; Milev et al., 2005; Schennach-Wolff et al., 2009). Milev et al. (2005) followed-up a cohort of first episode psychotic patients for 7 years, and found that negative symptoms explained the major part of the variance of functioning, indicating the devastating persistent role of this kind of symptoms. Less attention has been given to the influence of positive symptomatology, but it also seems to play an important role on determining global functioning (Norman et al., 1999; Racenstein et al., 2002; Mohamed et al., 2008; Heinrichs et al., 2009). Hence, Wittorf et al. (2008) in a longitudinal study with patients suffering from schizophrenia found that positive symptoms consistently predicted global functioning 1 year after hospital discharge. Moreover, Goldman et al. (1999) in a study with schizophrenic patients reported that global functioning had stronger correlations with positive than negative symptoms. However, the same authors (Goldman et al., 1999) also reported that depressive symptoms did not show any correlation with global functioning, although Mueser et al. (1997) suggest that depressive symptoms do determine vocational functioning in their longitudinal study. Furthermore, a European multicentre study (Gaite et al., 2005—the Epsilon Study) reported that all three types of symptoms, negative, positive and affective, explained most of the variance of global functioning. The effect size of symptomatology in this study was consistent across the five centres that took part, suggesting that the role of symptomatology on determining global functioning of persons suffering from psychotic disorders is unlikely to be affected by cultural and other differences across nations.

Whilst many clinical decisions in clinical practise with persons suffering from psychotic disorders depend on their psychopathological assessment, there is still a relative shortage of prospective studies that explore how psychopathological symptoms influence the patients' global functioning. In this analysis, we set out to study such influence from a broad psychopathological perspective, taking into account the role of potential confounders and using a large European cohort of persons suffering from ICD-10 psychosis who were followed-up for three months after an acute episode leading to in-patient admission.

## 2. Materials and methods

This paper derives from the database of the project "European Evaluation of Coercion in Psychiatry and Harmonisation of Best Clinical Practise" (Acronym: EUNOMIA). A detailed description of the EUNOMIA project methodology can be found elsewhere (Mastrogianni et al., 2004; Kallert et al., 2005; Priebe et al., 2010; Raboch et al., 2010; Fiorillo et al., 2011). In brief, its main clinical aim was to assess the practise of legally involuntary admissions to psychiatric hospitals and their outcomes. Its naturalistic and epidemiological design was implemented at 13 centres in 11 European countries (Bulgaria, Czech Republic, Germany, Greece, Spain, Italy, Lithuania, Poland, Slovakia, Sweden, United Kingdom) and one associated (Israel). Tel Aviv in Israel was originally included, but omitted from this analysis because of inadequate study implementation. 2326 patients, who were admitted to acute wards in these centres, were evaluated during the period 2003–2005. Patients were excluded if they have been admitted to a special unit only for forensic psychiatric or intoxicated reasons or suffered from eating disorders or dementia. Each patient was assessed at three time points: within the first seven days of admission, at 4 weeks and at 3 months after admission, independently of his/her current living situation. Assessments in all sites were carried out by researchers who had both local and joint international common training sessions on administering and rating all study assessment scales and instruments.

### 2.1. The sample

Out of the initial sample of 2326 patients, all 1888 with a diagnosis of psychotic disorder (i.e., F20–29 diagnosis according to ICD-10 as established by psychiatric reports within the first seven days of admission and the clinical history of every patient) were included in the present analysis. Other inclusion criteria included being between 18 and 65 years of age, having complete data for the variables included in this analysis (see below) and having a signed informed consent form for participation in this project. Patients with incomplete data of global functioning or symptomatology were excluded.

#### 2.1.1. Outcome variable: the GAF measurement of functionality

The outcome variable in this analysis was patients' global functioning as evaluated using the Global Assessment of Functioning scale (GAF) (Goldman et al., 1992). GAF was measured twice (at months 0 and 3) and main outcome used was time 1 (month 3) measurements adjusted by time 0 (month 0) GAF ratings. This scale constitutes axis V of the Diagnostic and Statistical Manual for Mental Disorders 4th edition (DSM-IV) (American Psychiatric Association, 1994) and assesses patient's social occupational and psychological functioning in a hypothetical continuum of 1 to 100 points, which is divided in 10 ranges of 10 points, although a single score that represents patient's level of functioning is obtained. All interviewers were trained using a standardised method to train GAF consisting of rating of some 72 GAF vignettes that were jointly rated by interviewers that had received first a local training session and then a common international video training session (in English). The GAF

inter-rater reliability for the whole training process was good with an interclass correlation coefficient of 0.74 (ICC = 0.74).

*2.1.2. Independent variables*

For the specific purposes of this analysis, we used the following independent variables:

a) Data on age, sex, education, civil status, study country, pharmacological treatment and previous hospital admissions were obtained via systematic inspection of the patient's medical records.
b) To examine the presence of psychopathology, the expanded Brief Psychiatric Rating Scale-24 item version (BPRS-E; Lukoff et al., 1986) was administered. This scale is broadly used by clinics for evaluating psychotic symptoms through an interview with the patients. Six new items were added to the original scale (Overall and Gorham, 1962), in order to gain more sensitivity to a wide range of psychotic and affective symptoms, as this version allows further exploration of manic symptoms (Ventura et al., 2000). Good psychometric properties of this improved version were reported earlier (Burlingame et al., 2006). In our study, an inter-rater reliability (intraclass correlation coefficient) of 0.78 was achieved between researchers of the various centres.

*2.2. Statistical analyses*

For the present analysis, assessment scores at time of admission and 3 months later were used. Analyses were carried out taking into account ratings of the GAF scale at both time points, plus the BPRS scores, sociodemographic and clinical variables obtained at the baseline assessments. Four types of statistical analyses were performed using the SPSS 15 for Windows: a descriptive analysis, a principal component factor analysis and two sets of multiple regression analysis (univariate and multivariate). The first was a descriptive analysis including the psychosocial and clinical characteristics of the sample and its distribution on the various diagnostic subtypes of psychotic disorder according to the ICD-10. The second was a principal component analysis (PCA) with Kaiser varimax rotation of the BPRS, determining the sedimentation curve, standard deviation and variance. The 24 items of the scale were distributed to 6 categories and the weight of each item was calculated for each one of the 6 dimensions found. The third was a set of multiple regression analyses, to determine cross-sectional determinants of GAF scores at initial assessment. This included a univariate analysis, where psychopathologic dimensions of BPRS were exclusively entered in the regression, and a multivariate analysis where BPRS dimensions at initial assessment and the rest of psychosocial variables (age, sex, civil status, medication, study country) were entered together in the model. The fourth included a set of regression analysis that served for examining if psychopathological dimensions at admission determine GAF scores three months later. This time, in the univariate multiple regression, BPRS dimensions at admission were entered as the independent variables, and in the multivariate multiple regression, BPRS dimensions together with other psychosocial variables (age, sex, civil status, medication, study country) and GAF scores at admission were entered in the model. Results of this second set of regression analysis represent the change in patients' global functioning from initial assessment to follow up.

## 3. Results

*3.1. Sociodemographic, clinical and psychosocial characteristics*

1888 patients having an ICD-10 diagnosis of non-affective psychotic disorder (F20–F29) who have been admitted in an acute psychiatric ward were included in the analysis. Out of the initial sample, 1036 were successfully followed-up three months later. Table 1 shows sociodemographic, clinical and psychosocial characteristics of the sample at admission and follow-up. Cohort participants assessed at baseline but who were lost to follow-up did not significantly differ from those fully completing the study on gender, marital status, age, treatment compliance or psychosis type, but tended to have higher scores on GAF and BPRS psychopathological dimensions.

*3.2. BPRS psychopathological dimensions*

The Principal Component Analysis (PCA) of the BPRS scores of our sample resulted in six principal components with Eigenvalues over 1.0 that explained 61.2% of the variance. After varimax rotation, these factors were identified as mania (Eigenvalue = 4.653), negative (Eigenvalue = 2.467), positive (Eigenvalue = 2.278), depressive (Eigenvalue = 2.180), agitation/cognitive (Eigenvalue = 1.827) and anxiety (1.306). Distribution of symptoms on psychopathologic dimensions is seen at Table 2.

*3.2.1. Cross sectional associations with global functioning at initial assessment*

When psychopathological dimensions were examined as possible cross-sectional determinants of global functioning, three of them (agitation/cognitive, negative and positive) were found to associate significantly with baseline global functioning. Such associations held

**Table 1**
Descriptive characteristics of the sample at admission (n = 1888) and follow-up (n = 1036).

| Sociodemographic characteristics | Mean (SD) | | Percentage | |
|---|---|---|---|---|
| | Admission | Follow-up | Admission | Follow-up |
| Sex | Male | | 56.3% | 54.9% |
| | Female | | 43.7% | 45.1% |
| Age | 38.8 (11.02) | 38.9 (10.98) | | |
| Age at leaving education | 18.4 (4.24) | 19.2 (4.21) | | |
| Civil status | Single | | 61.2% | 61.0% |
| | Married | | 21.7% | 21.5% |
| | Divorced | | 15.1% | 15.5% |
| | Widowed | | 2.0% | 8.6% |

Global functioning

| | Mean of GAF(SD) | |
|---|---|---|
| Study centre | Admission | Follow-up |
| Naples (Italy) | 41.28 (13.22) | 50.06 (15.51) |
| Granada and Málaga (Spain) | 38.05 (13.65) | 48.37 (15.89) |
| Wroclaw (Poland) | 37.08 (12.57) | 60.46 (15.42) |
| London (United Kingdom) | 33.91 (9.92) | 48.07 (13.82) |
| OErebro (Sweden) | 31.27 (11.57) | 43.34 (14.66) |
| Prague (Czech Republic) | 30.85 (13.30) | 63.59 (16.36) |
| Dresden (Germany) | 27.15 (8.61) | 51.8 (14.28) |
| Sofia (Bulgaria) | 26.33 (15.88) | 45.53 (15.81) |
| Vilnius (Lithuania) | 26.20 (9.89) | 45.08 (13.24) |
| Thessaloniki (Greece) | 23.85 (6.80) | 44.18 (18.25) |
| Michalovce (Slovakia) | 25.44 (10.49) | 47.71 (16.54) |
| Mean GAF Scores | 31.1 (13.55) | 49.66 (16.71) |

Clinical-psychopathologic characteristics

| | | Admission | Follow-up |
|---|---|---|---|
| Hospital admissions | 1st admission | 77% | |
| | Not 1st admission | 23% | |
| Medication compliance | | 86.6% | 86.2% |
| Diagnosis | Schizophrenia | 66.7% | 64.8% |
| | Schizoaffective | 16.7% | 18.3% |
| | Other psychosis | 16.6% | 16.9% |
| BPRS ratings | Mean (SD) | 2.1 (0.6) | 1.6 (0.46) |

SD: standard deviation.
GAF: global assessment of functioning.
BPRS: brief psychiatric rating scale.

**Table 2**
Psychopathological dimensions according principal component analysis of BPRS scores.

| Dimension | BPRS symptoms at admission | Load coefficient |
|---|---|---|
| Agitation/cognitive | Tension | .776 |
| | Uncooperativeness | .767 |
| | Disctractibility | .764 |
| | Motor hyperactivity | .752 |
| | Excitement | .710 |
| | Self neglect | .564 |
| | Disorientation | .542 |
| | Mannerisms and posturing | .526 |
| | Conceptual disorganisation | .525 |
| | Hostility | .446 |
| Negative | Blunted affect | .862 |
| | Emotional withdrawal | .809 |
| | Motor retardation | .690 |
| Positive | Unusual thought content | .783 |
| | Hallucinations | .698 |
| | Suspiciousness | .659 |
| | Bizarre behaviour | .476 |
| Depression | Suicidality | .804 |
| | Depression | .746 |
| | Guilt | .731 |
| Mania | Grandiosity | .826 |
| | Elevated mood | .786 |
| Anxiety | Somatic concern | .723 |
| | Anxiety | .574. |

significant after adjusting for other potential correlates and confounders of baseline global functioning as shown in Table 3.

*3.2.2. Prospective associations with global functioning*

Examining the prospective psychopathological predictors of global functioning at the 3-month follow-up, we found that the agitation/cognitive dimension accounted for 5% of the variance, the manic dimension for 1.4% and depressive for the 0.9% of the variance on prospective global functioning. No other symptomatic dimensions, including both positive and negative symptoms, were found to significantly predict global functioning. When other potential predictors of functionality were entered in the multivariate model we found no association between global functioning and having had a first admission, occupation and total length of illness, which were all hence excluded them from the analysis. However, better global functioning at baseline, younger age, female gender, married/coupled marital status, living in a southern study country and having a diagnosis of schizoaffective disorder (rather than schizophrenia or other non-affective psychosis) were all found to predict better global functioning three months after in-patient admission. Table 4 shows the most parsimonious predicting model for prospective global functioning (R-squared calculations estimate that the model explains 24.4% of outcome's total variance).

## 4. Discussion

The purpose of the present analysis was to investigate whether psychopathological symptom dimensions during acute non-affective psychotic episodes are independent predictors of global functioning three months later. We found evidence that psychopathological symptoms during an acute psychotic episode are robust and significant predictors of global functioning three months later. Thus, affective symptoms (either manic or depressive) predict better global functioning and agitation and cognitive symptoms are associated with poorer prospective global functioning. The longitudinal design of the study, the relatively large sample of persons suffering from ICD-10 non-affective psychosis and the inclusion of potential confounders in the multivariate analysis, make this a fairly novel report that measures how mental symptoms at the patient's maximum peak influence outcome. We also provide a comprehensive predicting model for global functioning valid not only for schizophrenia but also for other non-affective psychotic disorders that may be of use when planning follow-up care after discharge from an acute in-patient psychiatric unit (Fig. 1). Our results are also innovative in showing that agitation/cognitive symptoms, along with affective symptoms, seem to be more predictive of global functioning than the more traditionally scrutinised positive/negative dichotomy. We also replicate findings of a better outcome amongst females, those living in poorer-income countries and those with schizoaffective disorder rather than schizophrenia or other non-affective ICD-10 psychosis.

**Table 3**
Multivariate cross-sectional associations between psychopathological dimensions and of global functioning at admission.

| Associated factors | Coefficients | | |
|---|---|---|---|
| | β | t | p |
| BPRS negative dimension | −.176 | −7.983 | .0001 |
| BPRS positive Dimension | −.364 | −16.351 | .0001 |
| BPRS agitation/cognitive dimension | −.155 | −6.571 | .0001 |
| Sex | .118 | 5.278 | .0001 |
| Study country | .078 | 3.271 | .0001 |

p<.001.
BPRS: brief psychiatric rating scale.

**Table 4**
Prospective psychopathological predictors of global functioning adjusting by potential confounders at follow up.

| Predictors | Coefficients | | |
|---|---|---|---|
| | β | t | p |
| BPRS depression dimension | .065 | 2.325 | .020 |
| BPRS mania dimension | .096 | 3.391 | .001 |
| BPRS agitation/cognitive dimension | −.181 | −5.855 | .0001 |
| Sex | −.087 | −2.986 | .003 |
| Age on admission | −.081 | −2.575 | .010 |
| Marital status | .073 | 2.286 | .022 |
| Compliance with medication | −.146 | −5.347 | .0001 |
| Study country | −.135 | −4.557 | .0001 |
| GAF scores at admission | .391 | 13.892 | .0001 |
| Type of psychosis | .075 | 2.629 | .009 |

p<.001.
BPRS: brief psychiatric rating scale.

*4.1. Positive/negative symptoms and global functioning*

We found a cross-sectional association between positive symptomatology and global functioning at time of admission, in accordance with other studies (Heinrichs et al., 2009). However, we did not find a prospective association between positive symptoms and prospectively measured global functioning as opposed to previous reports (Goldman et al., 1999; Wittorf et al., 2008). We hypothesise that the influence of positive symptoms is higher when they are at its highest peak of expression (i.e., during admission) but not after three months, something supported by the well-known effectiveness of antipsychotic treatments when compliance is adequate (Sthal, 2009). A cross-sectional association between global functioning and negative symptoms was only apparent whilst during admission as reported earlier (Addington and Addington, 1999; Hofer et al., 2006; Villalta-Gil et al., 2006; Rocca et al., 2009). However, this association did not hold significant prospectively indicating its possible dependence on compliance with medication, which, in turn, was indeed a prospective determinant of global functioning. Previous findings of positive prospective associations between negative symptoms might be explainable by the absence of adjustment by potential confounders (medication, cognitive functioning) and/or other psychopathological dimensions (Herbener and Harrow, 2004; Milev et al., 2005) or by the use of different measures of psychopathology (Lindstrom, 1996; Schennach-Wolff et al., 2009). A lack of prospective effect for negative

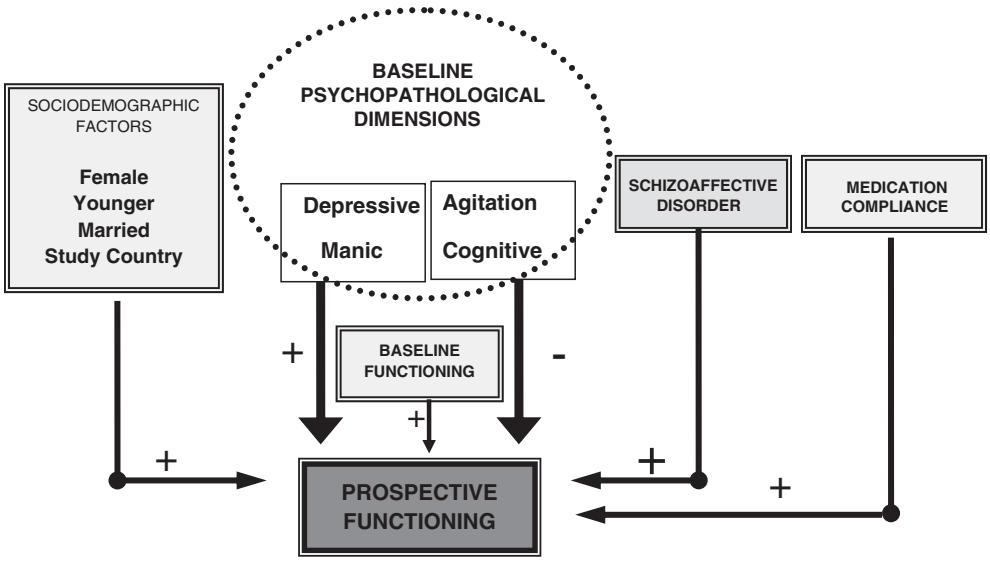


**Fig. 1.** Prospective model of psychopathological and clinical predictors of global functioning in patients with psychosis.

symptoms can also be explained by inclusion of some negative and cognitive symptoms in our agitation/cognitive factor which, in turn, is associated with poorer global functioning in our sample. Additionally, a classical long-term international study (Hawk et al., 1975; Breier et al., 1991) finding an association between negative symptoms and functioning reported it to be apparent only if the patient was medicated and might have been influenced by large sample attrition over the large follow-up period.

### 4.2. Affective symptoms and global functioning

Affective symptoms have been consistently associated with better prognosis in schizophrenia (Davidson and McGlashan, 1997) and the prospective role of depressive symptoms was also reported previously (Gaite et al., 2005—the Epsilon Study). We found that both depressive and manic symptoms (excluding tension/excitation, which emerged as an independent factor in our factor analysis) prospectively predict a better global functioning. Our findings also support the notion that restricted affect predicts poorer outcome (Carpenter and Strauss, 1991). In addition, this finding is agreeable with both clinical practise and classical description of less severe forms of psychotic symptoms, when mediated or congruent with an affective state (Sims, 1998; Salokangas, 2003).

### 4.3. Agitation and cognitive symptoms and global functioning

To the best of our knowledge, few previous studies have reported a discrete agitation/cognitive dimension, as separated from manic symptoms, when exploring psychopathology in a psychotic cohort (Nitsche and Kallert, 2007; Schützwohl et al., 2007). According to Ventura et al. (2000) whilst the BPRS might be fairly sensitive to detect agitation symptoms as motor hyperactivity and distraction. This could explain, along with the patients' acute state when psychopathologically assessed, why we found agitation/cognition to be such an important factor in our sample. Previous studies (Ventura et al., 2000; Ruggeri et al., 2005; Kopelowicz et al., 2008) had amalgamated within the same dimension what our study split into two discrete ones (i.e., manic and agitation) with, indeed, opposite effects on our outcome variable. We pose that the poorer global functioning predicted by agitation/cognitive symptoms may be due to the effects of more basic and less elaborated forms of psychopathology (agitation) that are less likely to respond to treatment. Nonetheless, some studies have previously reported that hostility symptoms do predict poorer outcome (Haro et al., 2008). In addition, the agitation/cognitive dimension also contains cognitive symptoms and they have previously been extensively reported as predictors of poorer outcome (Addington and Addington, 1999; Rössler et al., 2007).

### 4.4. Other factors and global functioning

Apart from the influence of psychopathological dimensions as determinants of global functioning, other factors also associate independently to global functioning in persons suffering from psychotic disorders. In particular, being a woman, married or coupled and of a younger age appears to predict a better global functioning three months later. Such findings are consistent with previous reports (Zipursky and Schulz, 2002; Gaite et al., 2005; Haro et al., 2008; Wittorf et al., 2008; Cotton et al., 2009). Place of residence, as defined by study country, also seems to determine global functioning, indicating perhaps a variety in quality of treatment across centres or the influence of family-based care which is known to be more extensive in southern than in northern European countries (Gaite et al., 2005). As previously reported (Miyamoto et al., 2003; Valencia et al., 2004), and fitting with clinical sense, adequate compliance with medication also predicts better functionality in our sample. Better compliance may also be a by-proxy of better insight which, in turn, has been reported as predictive of better outcome in an English prospective cohort of non-affective psychosis (Drake et al., 2007). Finally, within non-affective psychotic disorders, having a diagnosis of schizophrenia rather than schizoaffective or other non-schizophrenic psychosis had also been reported earlier as predictive or poorer outcome (Hawk et al., 1975; Breier et al., 1991).

### 4.5. Limitations and strengths

Some limitations should be taken into account when interpreting our results. First, the existing effect of psychopathology on global functioning three months after hospitalisation could be challenged by the limitation of GAF instrument, as it includes assessment of some mental symptoms. Potential collinearity of GAF with BPRS was minimised in our analysis by adjusting for baseline GAF scores at follow up, as it should take most of the common bits with baseline BPRS. The present analysis derives from a European project, an international project that was destined to examine coercive measures in psychiatry and quality of clinical practise (Mastrogianni et al., 2004;

Kallert et al., 2005; Priebe et al., 2010; Raboch et al., 2010; Fiorillo et al., 2011). The assessment of global functioning and its determinants was not specifically planned to serve the purposes of the study. Consequently, though a broad range of potential determinant variables was examined in this analysis, it was not possible to test the possible effect of variables known to influence functionality such as cognitive performance (Green et al., 2004), duration of untreated psychosis (Marshall et al., 2005), premorbid adjustment (Larsen et al., 2000) or other potential confounders (e.g. comorbidity, family-related factors, socioeconomic status etc.). Finally, attrition bias cannot be entirely ruled out although there were no statistical differences, between cohort participants and baseline and those who completed the full study assessments, as for most potential confounders. In addition, differences between these two groups on GAF and psychopathological dimensions might have been minimised by inclusion of these variables in the final multivariable models. Thus, there is a need for future studies that incorporate to their design such potential determinants of global functioning in addition to using longitudinal designs with representative samples of persons suffering from psychotic disorders.

On the other hand, the major strengths of this analysis are the implementation of a consistent study design in different countries, the use of trained researchers and the application of standardised and well-established assessment methods. Additionally, the inclusion of a relatively large number of persons suffering from psychotic disorders at initial stages of hospital treatment is of major importance, as engaging such type of patients in research can be most difficult (e.g. because of high symptom levels and poor motivation in involuntary patients). Moreover, a prospective design was implemented, using a relatively good follow-up rate for this type of challenging and difficult to research patients, although a longer follow-up might have thrown a more definite light on the topic. Generally, the importance of acute psychopathology on short-term global functioning is limited as only some symptoms (affective and agitation/cognitive) seem to exert a modest prospective effect. Thus, it is striking that the most scrutinised psychotic symptoms (i.e., positive or negative) do not predict global functioning even at a short-term three-month follow-up.

On the whole, our predicting model for global functioning is valid across several non-affective psychosis diagnoses and demonstrates that whilst some psychoses (i.e. schizoaffective) are associated with better outcome than others (i.e. schizophrenia), the model is compatible with a dimensional way of understanding psychosis as it can be foreseen from DSM-V early reports. Our results also suggest that assessing patients holistically during acute psychotic episodes, including agitation, cognitive and affective symptoms, and enhancing adherence, can help plan better-functioning follow-up care.

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**Contributors**

Eleni Petkari has reviewed the literature, written the first draught of the paper.

Ana M. Salazar-Montes has also helped in reviewing the literature and preparing data for edition and reporting as well as helping to prepare tables and figures in the paper.

Thomas W. Kallert was the principal investigator for the Eunomia Study and has supervised extensively both the field work and the preparation of the manuscript.

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Jorge A. Cervilla developed the study idea, has led all statistical analyses and has supervised and helped in writing the paper.

**Conflict of Interest**

The authors declare no conflict of interest.

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## References

Aas, I.M., 2010. Global Assessment of Functioning (GAF): properties and frontier of current knowledge. Ann Gen Psychiatry 7 (9), 20.

Addington, J., Addington, D., 1999. Neurocognitive and social functioning in schizophrenia. Schizophr. Bull. 25 (1), 173–182.

American Psychiatric Association, 1994. DSM-IV. Diagnostic and Statistical Manual of Mental Disorders. APA, Washington.

Breier, A., Schreiber, J.L., Dyer, J., Pickar, D., 1991. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. Arch. Gen. Psychiatry 48 (3), 239–246 Mar.

Burlingame, G., Seaman, S., Johnson, J., Whipple, J., Richardson, E., 2006. Sensitivity to change of the brief psychiatric rating scale-extended (BPRS-E): an item and subscale analysis. Psychol. Serv. 3 (2), 77–87.

Carpenter Jr., W.T., Strauss, J.S., 1991. The prediction of outcome in schizophrenia. IV: eleven-year follow-up of the Washington IPSS cohort. J. Nerv. Ment. Dis. 179 (9), 517–525 Sep.

Cotton, S.M., Lambert, M., Schimmelmann, B.G., Foley, D.L., Morley, K.I., McGorry, P.D., Conus, P., 2009. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. Schizophr. Res. 114 (1), 17–24.

Davidson, L., McGlashan, T.H., 1997. The varied outcomes of schizophrenia. Can. J. Psychiatry 42, 34–43.

Drake, R.J., Dunn, G., Tarrier, N., Bentall, R.P., Haddock, G., Lewis, S.W., 2007. Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. J. Clin. Psychiatry 68 (1), 81–86 Jan.

Fiorillo, A., De Rosa, C., Del Vecchio, V., Jurjanz, L., Schnall, K., Onchev, G., Alexiev, S., Raboch, J., Kalisova, L., Mastrogianni, A., Georgiadou, E., Solomon, Z., Dembinskas, A., Raskauskas, V., Nawka, P., Nawka, A., Kiejna, A., Hadrys, T., Torres-Gonzales, F., Mayoral, F., Björkdahl, A., Kjellin, L., Priebe, S., Maj, M., Kallert, T., 2011. How to improve clinical practice on involuntary hospital admissions of psychiatric patients: Suggestions from the EUNOMIA study. Eur. Psychiatry 26, 201–207.

Gaite, L., Vázquez-Barquero, J.L., Herrán, A., Thornicroft, G., Becker, T., Sierra-Biddle, D., Ruggeri, M., Schene, A., Knapp, M., Vázquez-Bourgona, J., EPSILON Group, 2005. Main determinants of Global Assessment of Functioning score in schizophrenia: a European multicentre study. Compr. Psychiatry 46, 440–446.

Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising Axis V for DSM-IV: a review of measures of social functioning. Am. J. Psychiatry 149, 1148–1156.

Goldman, M., Dequardo, R., Tandon, R., Taylor, S., Jibson, M., 1999. Symptom correlates of global measures of severity in schizophrenia. Compr. Psychiatry 40, 458–461.

Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J. Clin. Psychiatry 67, 3–8.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the right stuff? Schizophr. Bull. 26, 119–136.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72, 41–51.

Haro, J.M., Novick, D., Suarez, D., Ochoa, S., Roca, M., 2008. Predictors of the course of illness in outpatients with schizophrenia: a prospective three-year study. Prog. Neuro-psychopharmacol. Biol. Psychiatry 32, 1287–1292.

Harvey, P.D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R.C., Hoblyn, J., Davis, K.L., 1998. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am. J. Psychiatry 155, 1080–1086.

Harvey, P.D., Keefe, R.S.E., Patterson, T.L., Heaton, R.K., Bowie, R.C., 2009. Abbreviated neuropsychological assessment in schizophrenia: prediction of different aspects of outcome. J. Clin. Exp. Neuropsychol. 31, 462–471.

Hawk, A.B., Carpenter Jr., W.T., Strauss, J.S., 1975. Diagnostic criteria and five-year outcome in schizophrenia. A report from the International Pilot Study of schizophrenia. Arch. Gen. Psychiatry 32 (3), 343–347 Mar.

Heinrichs, R.W., Ammari, N., Miles, A., McDermid Vaz, S., Chopov, B., 2009. Psychopathology and cognition in divergent functional outcomes in schizophrenia. Schizophr. Res. 109, 46–51.

Herbener, E.S., Harrow, M., 2004. Are negative symptoms associated with functioning deficits in both schizophrenia and non-schizophrenia patients? A 10-year longitudinal analysis. Schizophr. Bull. 30 (4), 813–825.

Hofer, A., Rettenbacher, M.A., Widschwendter, C.G., Kemmler, G., Hummer, M., Fleischhacker, W.W., 2006. Correlates of subjective and functional outcomes in outpatient clinic attendees with schizophrenia and schizoaffective disorder. Eur. Arch. Psychiatry Clin. Neurosci. 256 (4), 246–255.

Kallert, T., Glöckner, M., Onchev, G., Raboch, J., Karastergiou, A., Solomon, Z., Magliano, L., Dembinskas, A., Kiejna, A., Nauwka, P., Torres-Gonzalez, F., Priebe, S., Kjellin, L., 2005. The EUNOMIA project on coercion in psychiatry: study design and preliminary data. World Psychiatry 4, 168–172.
Kopelowicz, A., Ventura, J., Liberman, R.P., Mintz, J., 2008. Consistency of brief psychiatric rating scale factor structure across a broad spectrum of schizophrenia patients. Psychopathology 41, 77–84.
Kurtz, M.M., 2006. Symptoms versus neurocognitive skills as correlates of everyday functioning in severe mental illness. Expert. Rev. Neurother. 6, 47–56.
Larsen, T.K., Moe, L.C., Vibe-Hansen, L., Johannessen, J.O., 2000. Premorbid functioning versus duration of untreated psychosis in one year outcome in first-episode psychosis. Schiz Res 45 (1), 1–9.
Lindstrom, L.H., 1996. Clinical and biological markers for outcome in schizophrenia: a review of a longitudinal follow-up study in Uppsala schizophrenia research project. Neuropsychopharmacology 14, 23S–26S.
Lukoff, D., Nuechterlein, K.H., Ventura, J., 1986. Manual for the expanded brief psychiatric rating scale. Schizophr. Bull. 12, 594–602.
Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., Croudace, T., 2005. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch. Gen. Psychiatry 62 (9), 975–983.
Mastrogianni, A., Georgiadou, E., Iosifidis, I., Kotrotsios, S., Karastergiou, A., the EUNOMIA team, 2004. The Eunomia study: European evaluation of coercion in psychiatry and harmonization of best clinical practice. Hell. Gen. Hosp. Psychiatry 3, 37–43.
Milev, P., Ho, B., Arndt, S., Andreasen, N., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am. J. Psychiatry 162, 495–506.
Miyamoto, S., Lieberman, J.A., Fleischhacker, W.W., Aoba, A., Marder, S.R., 2003. Antipsychotic drugs, In: Tasman, A., Kay, J., Lieberman, J.A. (Eds.), Psychiatry, 2nd edn. John Wiley & Sons, Ltd, Chichester, pp. 1928–1964.
Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J.A., Keefe, R.S.E., 2008. Relationship of cognition and psychopathology to functional impairment in schizophrenia. Am. J. Psychiatry 165, 978–987.
Moos, R.H., Nichol, A.C., Moos, B.S., 2002. Global Assessment of Functioning ratings and the allocation and outcomes of mental health services. Psychiatr. Serv. 53 (6), 730–737.
Mueser, K.T., Becker, D.R., Torrey, W.C., Xie, H., Bond, G.R., Drake, R.E., Dain, B.J., 1997. Work and non-vocational domains of functioning in persons with severe mental illness: a longitudinal analysis. J. Nerv. Ment. Dis. 185, 419–426.
Nitsche, I., Kallert, T.W., 2007. Standardized assessment of psychopathology by relatives of mentally disordered patients. Preliminary results of using the positive and negative syndrome scale to compare schizophrenic and affective disorders. Psychopathology 40 (4), 242–253.
Norman, R.M., Malla, A.K., Cortese, L., Cheng, S., Diaz, K., McIntosh, E., 1999. Symptoms and cognition as predictors of community functioning. A prospective analysis. Am. J. Psychiatry 156, 400–405.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.
Palmer, B.W., Heaton, R.K., Gladsjo, J.A., Evans, J.D., Patterson, T.L., Golshan, S., Jeste, D.V., 2002. Heterogeneity in functional status among older outpatients with schizophrenia: employment history, living situation, and driving. Schizophr. Res. 55, 205–215.
Patterson, T., Klapow, J., Eastham, J., Heaton, R., Evans, J., Koch, W., Jeste, D., 1998. Correlates of functional status in older patients with schizophrenia. Psychiatr. Res. 80, 41–52.
Priebe, S., Katsakou, C., Glöckner, M., Dembinskas, A., Fiorillo, A., Karastergiou, A., Kiejna, A., Kjellin, L., Nawka, P., Onchev, G., Raboch, J., Schuetzwohl, M., Solomon, Z., Torres-González, F., Wang, D., Kallert, T., 2010. Patients' views of involuntary hospital admission after 1 and 3 months: prospective study in 11 European countries. Br. J. Psychiatry 196, 179–185.
Raboch, J., Kalisová, L., Nawka, A., Kitzlerová, E., Onchev, G., Karastergiou, A., Magliano, L., Dembinskas, A., Kiejna, A., Torres-Gonzales, F., Kjellin, L., Priebe, S., Kallert, T.W., 2010. Use of coercive measures during involuntary hospitalization: findings from ten European countries. Psychiatr. Serv. 61, 1012–1017.
Racenstein, J.M., Harrow, M., Reed, R., Martin, E., Herbener, E., Penn, D.L., 2002. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10 year follow-up study. Schizophr. Res. 56, 95–103.
Rocca, P., Montemagni, C., Castagna, F., Giugiario, M., Scalese, M., Bogetto, F., 2009. Relative contribution of antipsychotics, negative symptoms and executive functions to social functioning in stable schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 33, 373–379.
Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., van Os, J., Gross, V.A., 2007 Mayy. Psychotic experiences in the general population: a twenty-year prospective community study. Schizophr. Res. 92 (1–3), 1–14.
Ruggeri, M., Koeter, M., Schene, A., Bonetto, C., Vázquez-Barquero, J.L., Becker, T., Knapp, M., Knudsen, H.C., Tansella, M., Thornicroft, G., The EPSILON study Group, 2005. Factor solution of the BPRS-expanded version in schizophrenic outpatients living in five European countries. Schizophr. Res. 75, 107–117.
Salokangas, R., 2003. Symptom dimensions and outcome in schizophrenia. World Psych. 2, 172–178.
Schennach-Wolff, R., Jäger, M., Seemüller, F., Obermeier, M., Messer, T., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Huff, W., Heuser, I., Maier, W., Lemke, M.R., Rüther, E., Buchkremerm, G., Gastpar, M., Möller, H., Riedel, M., 2009. Defining and predicting functional outcome in schizophrenia and schizophrenia spectrum disorders. Schizophr. Res. 113, 210–217.
Schützwohl, M., Kallert, T., Jurjanz, L., 2007. Using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) as a diagnostic interview providing dimensional measures: cross-national findings on the psychometric properties of psychopathology scales. Eur. Psych. 22 (4), 229–238.
Shamsi, S., Lau, A., Lencz, T., Burdick, K.E., DeRosse, P., Brenner, R., Lindenmayer, J., Malhotra, A.K., 2011. Cognitive and symptomatic predictors of functional disability in schizophrenia. Schizophr. Res. 126 (1–3), 257–264.
Sharma, T., Antonova, L., 2003. Cognitive function in schizophrenia. Deficits, functional consequences, and future treatment. Psych. Clin. North Am. 26, 25–40.
Sims, A., 1998. Symptoms in the Mind. W.B. Saunders, London.
Smith, T., Hull, J., Romanelli, S., Fertuck, E., Weiss, K., 1999. Symptoms and neurocognition as rate limiters in skills training for psychotic patients. Am. J. Psychiatry 156, 1817–1818.
Sthal, S., 2009. Sthal's Essential Psychopharmacology, 3rd. Cambridge University Press, New York.
Thaker, G.K., Carpenter, W.T., 2001. Advances in schizophrenia. Nat. Med. 7, 667–671.
Thornicroft, G., Tansella, M., Becker, M., Knapp, M., Leese, M., Schene, A., 2004. The personal impact of schizophrenia in Europe. Schizophr. Res. 69, 125–132.
Usall, J., Haro, J.M., Ochoa, S., Márquez, M., Araya, S., NEDES Group (Assessment Research Group in schizophrenia), 2002. Influence of gender on social outcome in schizophrenia. Acta Psychiatr. Scand. 106, 337–342.
Valencia, M.C., Ortega-Soto, H.A., Rodríguez, M., Gomez, L.C., 2004. (Article in Spanish). Estudio comparativo de consideraciones clínicas y psicoterapéuticas en el tratamiento biopsicosocial de la esquizofrenia. Primera parte. Salud Mental 27 (4), 47–53.
Vatnaland, T., Vatnaland, J., Friis, S., Opjordsmoen, S., 2007. Are GAF scores reliable in routine clinical use? Acta Psychiatry Scand. 115, 326–330.
Vázquez-Barquero, J.L., Cuesta, M.J., Herrera, S., Lastra, I., Herrán, A., Dunn, G., 1999. Cantabria first-episode schizophrenia study: three-year follow-up. Br. J. of Psychiatry 174, 141–149.
Ventura, J., Nuechterlein, K.H., Subotnik, K.L., Gutkind, D., Gilbert, E.A., 2000. Symptom dimensions in recent-onset schizophrenia and mania: a principal components analysis of the 24-item Brief Psychiatric Rating Scale. Psych. Res. 97, 129–135.
Ventura, J., Hellemann, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr. Res. 113, 189–199.
Villalta-Gil, V., Vilaplana, M., Ochoa, S., Haro, J.M., Dolz, M., Usall, J., Cervilla, J., NEDENA Group, 2006. Neurocognitive performance and negative symptoms: are they equal in explaining disability in schizophrenia outpatients? Schizophr. Res. 87, 246–253.
Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., Nienhuis, F.J., Walsh, D., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. Psychol. Med. 30, 1155–1167.
Willwhite, R.K., Niendam, T.A., Bearden, C.E., Zinberg, J., O'Brien, M.P., Cannon, T.D., 2008. Gender differences in symptoms, functioning and social support in patients at ultra high risk for developing a psychotic disorder. Schizophr. Res. 104, 237–245.
Wittorf, A., Wiedemann, G., Buchkremer, G., Klingberg, S., 2008. Prediction of community outcome in schizophrenia 1 year after discharge from inpatient treatment. Eur. Arch Psychiatry Clin. Neurosci. 258, 48–58.
World Health Organization, 1992. ICD-10: International Classification of Diseases, Mental and Behaviour Disorders 10th. Switzerland, Geneva.
Zipursky, R., Schulz, S., 2002. The Early Stages of Schizophrenia. American Psychiatric Publishing Inc., Washington (DC), pp. 33–54.