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The use of clinical and biological characteristics to predict outcome following First Episode Psychosis

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Abstract

Objective: Psychotic illnesses such as schizophrenia and other non-affective psychoses are heterogeneous in disease course and functional outcomes. We review evidence from investigations in clinical psychiatry, neuroimaging, neurocognition, and blood biomarker research suggesting that distinct bio-psycho-social patterns exist at the onset and during the early phase of a First Episode Psychosis (FEP), which can describe the risk of individual illness progression and functional trajectories.

Method: A selective literature review was performed on articles drawn from Medline searches for relevant key words. A simulation model was constructed from data derived from two recent publications, selected as examples of studies that investigated multivariate predictors of long-term outcome following FEP.

Results: We illustrate how illness trajectories following FEP could be described based on multimodal sociodemographic, clinical, psychological, and neurobiological information. A clinical modeling simulation shows that risk trajectories for achieving long-term favorable or unfavorable outcomes can differ significantly depending on baseline characteristics in combination with MRI and functional measurements within 6 months of disease onset.

Conclusions: Multimodal trajectory modeling may be useful to describe longitudinal outcomes following FEP. Rich longitudinal data on predictors and outcomes, and better integration of multimodal (sociodemographic, clinical, psychological, biological) data, are required to operationalize this approach. This technique may improve our understanding of course of illness and help to provide a more personalized approach to the assessment and treatment of people presenting with FEP.

Keywords

Schizophrenia, first-episode psychosis, trajectories, predictive modeling, functioning

Introduction

Long-term follow-up studies in non-affective psychoses such as schizophrenia suggest that illness course and psychosocial outcomes differ considerably between people diagnosed with the disorder (Harding et al., 1987; Hegarty et al., 1994; Huber, 1997; Levine et al., 2011; Rangaswamy, 2012; Thara, 2004). These studies also suggest that the longitudinal severity of 'positive' clinical symptoms, such as delusions and hallucinations, and people's ability to live productive lives is only weakly correlated (Alvarez-Jimenez et al., 2012). In the face of illness heterogeneity (Alvarez-Jimenez et al., 2011; Banati and Hickie, 2009; Strauss and Carpenter, 1972), the question arises whether individual prognosis could be predicted at an early stage of the illness, to assist personalized treatment decisions.

Developmentally, schizophrenia has been associated with a set of subtle 'lesions' of the brain and other organ systems, which can be picked up by morphometry

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(Waddington et al., 1999), brain imaging (Pantelis et al., 2005), electrophysiology (Wolwer et al., 2012) and neurocognitive testing (De Herdt et al., 2013) long before the illness manifests itself, seem progressive in nature, and appear to be mediated by a genetic predisposition and by environmental influences. How these biological and behavioral correlates of non-affective psychoses, which are generally non-specific in relation to the diagnostic construct, correspond with 'good' or 'poor' illness course and functional outcomes is largely unknown. Over the recent years, considerable research activity addressing this question has generated an array of candidate 'prognostic predictors' from various lines of investigation. The difficulty with these data has been that individual candidate predictor variables for illness course and outcome have remained, in most cases, poorly replicated or too non-specific to be of any value for clinical practice, even when a large number of potential risk factors were modeled (Baune and Thome, 2011; Gaebel et al., 2014; Moller et al., 1986).

In this article, we seek to address the question whether it might be possible to combine individual 'predictor variables' from different modalities of investigation (e.g. clinical psychological, social, biological, imaging), to arrive at useful models that could stimulate further research and have the potential for translation into clinical practice. We review recent findings from the fields of clinical science, neurocognition, neuroimaging, and serum proteomics, which have produced data of potential interest for this process. We then discuss a structured translational approach to integrating these findings, focusing on the description of trajectories of illness progression and functional outcome in schizophrenia. Finally, we present an example, based on published data, of how such integration could produce a clinically informative decision aid.

Methods

Literature review

A selective literature review was performed on articles drawn from Medline searches for relevant key words. These included 'schizophrenia', 'psychosis', 'first episode', 'outcome', 'trajectory', 'longitudinal', 'prediction', and 'functioning' for the relevant areas of 'neuroimaging', 'cognition', and 'blood biomarkers'. Reference lists of relevant articles were reviewed for further publications.

Modeling

A simulation model was constructed from data published in two recent papers (Alvarez-Jimenez et al., 2012; Mourao-Miranda et al., 2012). No original data were accessed for our simulation. Publications were selected as examples of studies that investigated multivariate predictors of 'good' or 'poor' long-term outcomes following non-affective FEP, expressed by the proxy concepts of full functional recovery (FFR) at 7.5 years' follow-up ('good' outcome) (Alvarez-Jimenez et al., 2012) and intermittent illness (relatively 'good' outcome) versus continuous course ('poor outcome') at 6.5 years' follow-up (Mourao-Miranda et al., 2012). Positive and negative likelihood ratios (LRs) were calculated from the published data. In biomedical statistics, LRs constitute one of the best measures of diagnostic accuracy (McGee, 2002). Positive LRs (LR+) are calculated by the formula LR+ = sensitivity/(1−specificity), that is, the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive. Negative LRs are calculated by the formula LR− = 1−sensitivity/specificity, that is, the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative. Therefore, a positive LR of a test describes the ability of a positive result to increase the probability of a disease, and is ideally much larger than 1. In contrast, the negative LR of a test describes the ability of a negative result to decrease the probability of a disease, and is ideally as close to zero as possible (Sox et al., 2013).

For our model, positive and negative LRs for statistically significant clinical and demographic predictors of FFR at 7.5 years post FEP were calculated from data extracted from Álvarez-Jiménez et al. (Table 1). For the purpose of this illustrative model, we used all identified univariate predictors for FFR (female gender, post-secondary education, good insight, good premorbid adjustment, and independent living), even though only female gender statistically survived adjustment for potential confounders in the original study. We used the pre-test odds for FFR (0.35) from this sample as the initial odds of 'good' outcome at FEP for the model. These results were combined with data from a study using a support vector machine (SVM) MRI model, which predicted continued versus intermittent course of illness from MRI assessment at time of FEP (Mourao-Miranda et al., 2012). SVM is a type of machine learning, and allows categorization of specific features of an individual's data, for instance the pattern of grey or white matter volume on structural neuroimaging, into a predefined group using a classification algorithm, developed on a training data set. The technique makes it possible to draw diagnostic or prognostic conclusions for an individual patient by analyzing their individual test results against findings derived from case–control analyses (Orru et al., 2012).

LRs were calculated for prediction of intermittent versus chronic illness course in schizophrenia at 6.2 years. For the purpose of this simulation, we considered chronic illness course at 6.2 years to equate to 'poor' long-term outcome, and intermittent course to 'good' outcome, according to the suggestions of the authors of the original study.

In a first step, we simulated cases with low (0.07), medium (0.48), and high (0.83) probability of

Table 1. Predictors of good long-term outcome following FEP.

Predictor	TP	FP	TN	FN	Sensitivity	Specificity	LR+	LR−
Female[a]	22	34	121	32	0.41	0.78	1.86	0.76
Post-secondary education[a]	17	24	131	37	0.31	0.85	2.03	0.81
Insight good at FEP[a]	22	40	115	32	0.41	0.74	1.58	0.80
Good pre-morbid social adjustment or work history[a]	43	98	57	11	0.80	0.37	1.26	0.55
Independent living at FEP[a]	19	29	126	35	0.35	0.81	1.88	0.80
MRI[b]	-	-	-	-	0.71	0.68	2.22	0.43
Negative symptom remission at 8 months post FEP[c]	22	42	113	32	0.41	0.73	1.50	0.81
FFR at 8 months post FEP[c]	22	15	140	32	0.41	0.90	4.21	0.66

FN: false negative; FP: false positive; LR+: positive likelihood ratio, LR−: negative likelihood ratio; TN: true negative; TP: true positive.
[a]Baseline clinical and demographic predictors of FFR at 7.5 years (Alvarez-Jimenez et al., 2012).
[b]Baseline MRI: Grey Matter Volume – Support vector machine model distinguishes chronic versus intermittent course at 6 years with main differences in cingulate and parahippocampal gyri, basal ganglia, and thalami (Mourao-Miranda et al., 2012).
[c]Clinical predictors at 8 months post FEP of FFR at 7.5 years (Alvarez-Jimenez et al., 2012).

'good' outcome at FEP, by selecting combinations of Alvarez-Jimenez et al.'s clinical predictor LRs for the odds ratio model (Alvarez-Jimenez et al., 2012). For 'high probability of good outcome', we constructed a hypothetical patient who tested positive for all favorable clinical characteristics, and we used the positive LRs for these parameters in the model. Therefore, our hypothetical 'high probability of good outcome' patient was female (LR+=1.86), and had post-secondary education (LR+=2.03), good insight at FEP (LR+=1.58), a history of good premorbid adjustment (LR+=1.26), and a history of independent living (LR+=1.88) (Table 2). In contrast, the hypothetical 'low probability of good outcome patient', constructed using negative LRs, was male (LR−=0.76), had no post-secondary education (LR−=0.81), had poor insight at FEP (LR−=0.8) and poor premorbid adjustment (LR−=0.55), and was not living independently (LR−=0.8). A third 'intermediate' patient was constructed by mixing positive and negative LRs. This patient was female (LR+=1.86), had post-secondary education (LR+=2.03) and good insight at FEP (LR+=1.58), but demonstrated poor premorbid adjustment (LR−=0.55) and was not living independently (LR−=0.8) (Table 2).

In a second step, modeling a second mode of investigation at time of FEP, we used calculated LR+ and LR− to determine the probabilities of 'good' and 'poor' outcomes based on MRI findings. In a third step, simulating a third investigation at 8 months post FEP (Alvarez-Jimenez et al., 2012), LRs for functional status combined with negative symptoms status at 8 months were added to the odds ratio model.

The Simulation model to calculate the probability of 'good' and 'poor' outcomes at 7.5 years is as follows:

Odds of 'good' outcome at 7.5 years = odds of FFR at FEP × (LR gender × LR post-secondary education × LR insight × LR premorbid function × LR independent living) × LR MRI × (LR negative symptom remission at 8 months post FEP × LR FFR at 8 months post FEP). Probability of 'good' outcome at 7.5 years = odds of 'good' outcome at 7.5 years/(1+ odds of 'good' outcome at 7.5 years). We then plotted each of these probabilities in a tree diagram.

Results

Clinical predictors of illness course and functional outcome following FEP

Various proxy definitions for 'good' and 'poor' outcome following a first episode of non-affective psychoses exist in the literature. 'Good' outcomes are approximated by the concepts of FFR, full psychosocial recovery, and non-chronic course of illness. Because consensus criteria for these concepts are lacking, researchers conducting outcome studies in psychotic disorders have tended to formulate their own definitions of 'good' and 'poor' outcomes.

Danish researchers involved in the OPUS trial defined 'full psychosocial recovery' as a) having achieved remission from psychotic and negative symptoms over the last 2 years, b) no hospitalization or admission to a supported housing facility during this time, c) a Global Assessment of Functioning (GAF) score over 60, and d) engagement in competitive employment or study (Albert et al., 2011). Using these criteria, researchers found that female gender, higher age of onset, good pre-morbid adaptation, growing up with both parents, and low levels of negative symptoms at onset were predictors of full psychosocial recovery 5 years after

Table 2. Hypothetical patients constructed for modeling.

	Gender[a]	Post secondary education[a]	Good insight at FEP[a]	Good adjustment at FEP[a]	Independent living at FEP[a]
Patient 1 'high probability of good outcome' P =0.83	Female (LR+ =1.86)	Present (LR+ =2.03)	Present (LR+ =1.58)	Present (LR+ =1.26)	Present (LR+ =1.88)
Patient 2 'poor probability of good outcome' P =0.07	Male (LR- =0.76)	Absent (LR- =0.81)	Absent (LR- =0.8)	Absent (LR- =0.55)	Absent (LR- =0.8)
Patient 3 'intermediate probability of good outcome' P =0.48	Female (LR+ =1.86)	Present (LR+ =2.03)	Present (LR+ =1.58)	Absent (LR- =0.55)	Absent (LR- =0.8)

LR+: positive likelihood ratio; LR-:negative likelihood ratio
[a]Baseline clinical and demographic predictors of FFR at 7.5 years (Alvarez-Jimenez et al., 2012)

FEP, which was observed in 15% of patients (Albert et al., 2011). Females, in this patient sample, were significantly more likely than males to reach a state of recovery 5 years after FEP, expressed by higher levels of social functioning and a greater tendency to be employed or in education, to live with children, and to be compliant with medication (Thorup et al., 2014). In contrast, male gender, poor premorbid functioning, and more severe psychotic symptoms and negative symptoms at baseline predicted a continuous illness course (a proxy for 'poor' outcome), affecting 13% of patients of the same cohort (Bertelsen et al., 2009).

In an Australian longitudinal cohort of 274 FEP patients, FFR was defined as a) appropriate interpersonal relationships with people outside the family, b) engagement in paid employment, study, or role-appropriate home-making, c) success in fulfilling a chosen role, and d) regular participation in basic living tasks. Similar to the Danish study, female gender was found to be associated with FFR at 7.5 years following FEP (Alvarez-Jimenez et al., 2012). Other clinical baseline characteristics predictive of FFR, such as post-secondary education, independent living arrangements, good insight, high pre-morbid adjustment, and low baseline negative symptoms, did not statistically stand following adjustment for potential confounders known to be associated with functioning. In the same sample, duration of untreated psychosis (DUP) shorter than 60 days and absence of parental loss significantly predicted remission without relapse (a proxy for 'good' outcome) at 7.5 years' follow-up (Alvarez-Jimenez et al., 2011). DUP was also a strong baseline predictor for functional outcomes, expressed as overall functioning (GAF), frequency of social contacts (Strauss-Carpenter Level of Functioning Scale), and quality of life (Quality of Life Scale) at 8 years' follow-up in an Irish cohort (Crumlish et al., 2009).

Effective response to antipsychotic treatment in FEP has emerged as an important predictor of remission and recovery rates (Alvarez-Jimenez 2011), and can be identified as early as 2 weeks into treatment (Emsley et al., 2011). Using Growth Mixture Modeling (GMM) for Positive and Negative Symptom Scores (PANSS) in the first 12 weeks of treatment for FEP, Case et al. (2011) were able to identify four distinct patterns of early treatment response to olanzapine or risperidone. Rapid response to treatment strongly correlated with the ultimate, longer-term treatment success. Patients with a family history of psychosis, longer DUP, poor premorbid functioning, and lower severity of psychotic symptoms at intake have a reduced likelihood of responding early to antipsychotic treatment (Crespo-Facorro et al., 2013). Recent evidence suggests that these relationships are complex and that predictor variables influence positive, disorganized, and negative symptoms differentially (Pelayo-Teran et al., 2014).

Another emerging predictor for long-term illness course and outcome in schizophrenia is the functional status achieved within 12–24 months of FEP onset, which strongly predicted long-term functional recovery in Australian (Alvarez-Jimenez et al., 2012), Danish (Bertelsen et al., 2009), and Irish (Crumlish et al., 2009) cohorts. While the presence of negative symptoms of schizophrenia after 12–24 months worsened the functional prognosis significantly in these studies, this was not the case for residual positive symptoms.

Neurocognitive predictors of illness course and outcome following FEP

Cognitive impairment is present in the majority of individuals with schizophrenia and other non-affective psychoses, albeit significant heterogeneity between patients exists. On an individual basis, deficits appear to be relatively stable across the course of illness (Bora and Murray, 2014). We searched the literature for specific cognitive parameters, assessable at first presentation, that are associated with illness course and functional outcomes following FEP.

In FEP, measures of verbal fluency, memory, and social cognition can predict remission (Ayesa-Arriola et al., 2013; Simon et al., 2012) and relapses (Rund et al., 2007) within

the first 2 years of illness. Impairment in verbal memory predicts persistent negative symptoms and functional outcomes (Faerden et al., 2013; Hovington et al., 2013).

In clinically stable patients treated with clozapine, verbal working memory and attention were found to be better predictors of functional outcomes, such as employment, than psychotic symptoms (Kaneda et al., 2010). Similarly, patients with better cognitive functioning post-stabilization are more likely to experience functional recovery across a number of outcome domains, such as social interactions, work, and housing (Robinson et al., 2004). However, neurocognitive deficits alone cannot exclusively explain the variance in everyday functional impairments of people with severe mental illness (Green, 1996; Green et al., 2000), and may only predict certain functional domains. Therefore, cognitive assessments on their own are likely insufficient when attempting to predict the functional course of psychiatric illness (Harvey et al., 2012), and need to be considered in combination with other patient characteristics. For example, 'functional capacity' has recently been suggested as an independent construct, which can be assessed with separate assessment tools (Harvey et al., 2012). Functional capacity was shown to be strongly mediated by psychological characteristics such as a person's self-efficacy, defined as a person's belief that they can successfully perform a certain task (Cardenas et al., 2013). The example highlights the complexity of relationships between neurocognitive performance, real-world functional outcome, and psychosocial mediating factors, which need to be considered when conceptualizing descriptive models of illness course and outcome, as discussed later in this article.

Neuroimaging predictors of illness course and functional outcome following FEP

It is now generally accepted that schizophrenia is associated with structural brain abnormalities, which can be detected with neuroimaging technology at all stages of the illness (Pantelis et al., 2005).

Numerous studies have demonstrated a correlation between the extent of abnormal grey matter and cerebrospinal fluid (CSF) volumes in unmedicated patients at first presentation, and functional longitudinal outcomes (de Castro-Manglano et al., 2011; Milev et al., 2003; Mourao-Miranda et al., 2012). A large recent meta-analysis of over 18,000 individuals with schizophrenia (Haijma et al., 2013) concluded that 75% of the volume deficits in grey and white matter that were thought to be characteristic for chronic schizophrenia (Glahn et al., 2008) are detectable already at the onset of FEP (de Castro-Manglano et al., 2011; Milev et al., 2003; Mourao-Miranda et al., 2012). An analysis using an SVM whole-brain classification approach was able to distinguish, at baseline, FEP patients who would develop a continuous illness course from those with an episodic course, achieving sensitivity and specificity values around 70% (Mourao-Miranda et al., 2012). Authors approximated continuous illness course to 'poor' outcome, and episodic illness course to 'good', or favorable, outcome. Anatomically, the changes distinguishing the groups were most pronounced in the cingulate and parahippocampal gyri, the basal ganglia, and the thalami.

In a study assessing treatment response in FEP over 12 weeks, researchers demonstrated that non-responders, compared with responders, showed prominent baseline hypogyria of the bilateral insular, left frontal, and right temporal regions as assessed by unbiased whole-brain estimates of three-dimensional gyrification (Palaniyappan et al., 2013). Another group found that reduced grey matter concentrations in the parahippocampal cortex bilaterally (Bodnar et al., 2011; Bodnar et al., 2012b), as well as exaggerated positive activation of the posterior cingulate on functional magnetic resonance imaging (fMRI) in response to a visual encoding task (Bodnar et al., 2012a), were characteristic of patients who did not remit within a year of treatment. In the same sample of FEP patients, participants presenting with persistent negative symptoms after 1 year of treatment displayed at baseline reduced grey matter in the right frontal medial-orbital gyrus and right parahippocampal gyrus (Benoit et al., 2012).

Patients who respond to antipsychotic treatments demonstrate an enhanced capacity for striatal pre-synaptic dopamine synthesis, which is detectable via positron emission tomography (PET) (Demjaha et al., 2012). In contrast, treatment-resistant patients have striatal signatures undistinguishable from healthy controls.

Accounting for the global medication effects on brain imaging parameters that have been associated with the use of antipsychotics (Mamah et al., 2012), longitudinal imaging data now suggest that progressive volume loss following FEP occurs in a subset of patients, particularly during the early years following illness onset (Andreasen et al., 2011). One might speculate that this subgroup, showing progressive grey matter loss beyond global medication effects, is particularly vulnerable to prolonged psychotic relapses and to the gradual development of treatment resistance (Andreasen et al., 2013).

Conversely, recent studies suggest another subgroup of patients, who are able to regenerate brain structure and function following FEP. Measuring hippocampal volumes of FEP patients and healthy controls over 6 years, Lappin et al. (2014) found that 29% of FEP subjects and 22% of controls displayed bilateral hippocampal volume increases (HVI) over time, a phenomenon that had previously been reported in psychotic patients (Schaufelberger et al., 2011). Strikingly, the ability to 'grow' hippocampal volume was, for FEP patients, strongly associated with favorable functional and cognitive outcomes after 6 years.

These cross-sectional and longitudinal imaging markers are clearly in need of independent replication, and need to be carefully evaluated against the known effects of psychotropic medications on neuroimaging measures. Nevertheless,

these investigations point to an emerging array of cross-sectional and longitudinal neuroimaging markers with the potential to assist the description of illness course and outcome following FEP and in the formulation of prognostic models for non-affective psychoses.

Blood biomarkers as predictors of illness course and outcome following FEP

The search for diagnostic and prognostic biomarkers from peripheral blood has yielded some promising results over the last decade, due to increased technical capabilities of genomic, transcriptomic, proteomic, metabolomic, and cell biologic approaches. These investigations have culminated in the detection of distinct patterns of protein expression and candidate cellular mechanisms of psychiatric disorders in post-mortem brain and peripheral tissues (English et al., 2011; Focking et al., 2011; Ramshaw et al., 2013; Schubert et al., 2012). Test batteries using protein markers to differentiate people with schizophrenia from those with other psychiatric disorders and from healthy controls have also been proposed and validated (Schwarz et al., 2010; Schwarz et al., 2012a). What remains outstanding is the translation of this knowledge into standardized assays with truly meaningful clinical applications such as diagnostic stratification, prediction of medication response, and treatment monitoring (Weickert, 2013).

Some recent exemplary studies give a first impression of how these assays may look, and how they may contribute to future clinical practice. Schwarz et al. (2012b) followed FEP patients for 25 months, and found that differential expression of a small number of common serum proteins at first presentation predicted the response time to antipsychotic medication, and differentiated a group of patients suffering early relapse. In a subsequent study, the same group investigated serum protein signatures in medication-naïve FEP patients, and were able to define two 'molecular' subgroups according to common clusters of differentially expressed proteins, namely, a group with aberrant components of the immune system and a group with disturbed growth factors and hormones (Schwarz et al., 2014). Each subgroup represented about 20% of the total sample. It will be an important next step in research and clinical translation to investigate whether these subgroups based on a molecular classification present useful subgroups for predicting treatment response and prognosis.

This field of research is clearly still in its infancy, and findings warrant rigorous evaluation and replication. However, with the systematic application of high-throughput biomarker approaches in well-characterized and longitudinally followed psychosis patient cohorts, the relationships between patterns of protein expression, clinical trajectories, cognitive performance, brain structure, and treatment response will become ever clearer, and may yield serum biomarkers that can help describe the course and outcome following FEP.

Description of disease and functional trajectories following FEP based on multimodal sociodemographic, clinical, psychological, and neurobiological information

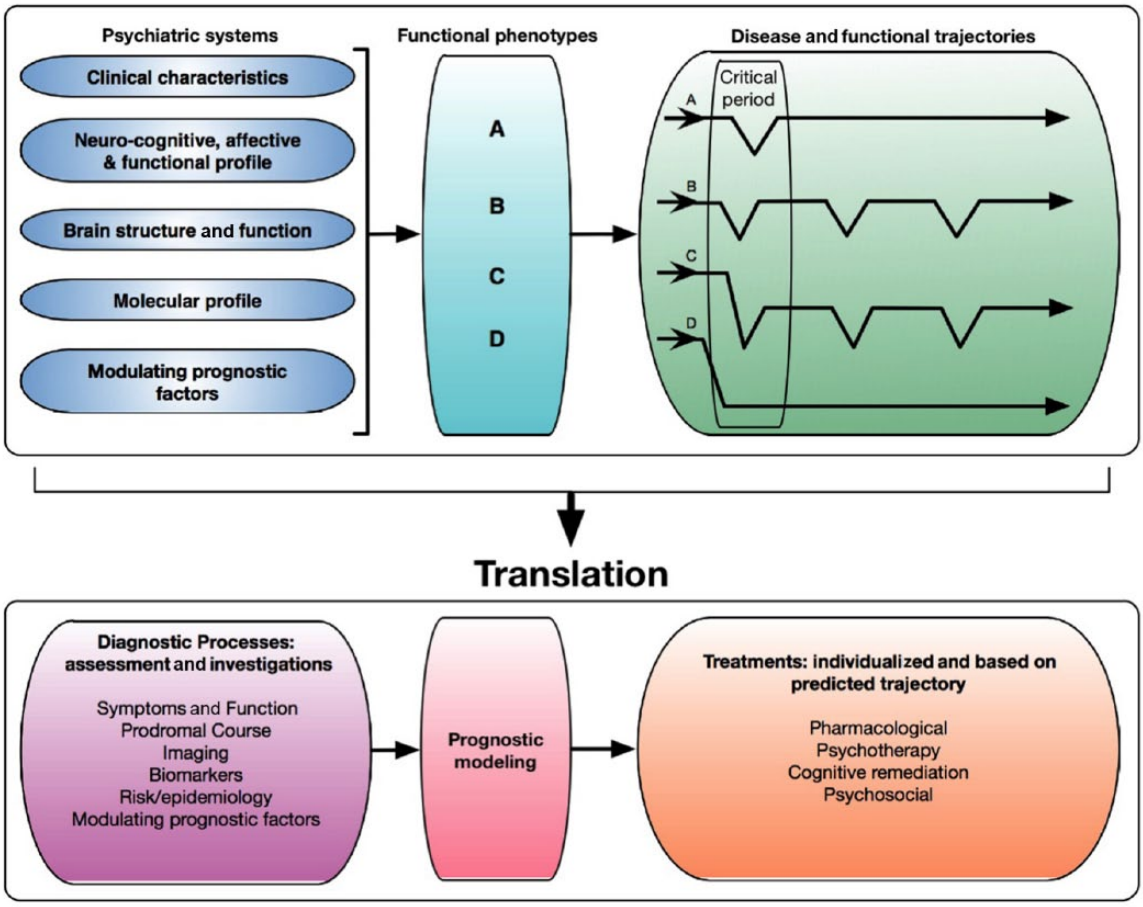
Historically, predictive modeling in psychiatry has largely been limited to models built from clinical variables (Moller et al., 1986). In order to achieve reliable prognostic statements, however, predictive models based on these clinical parameters alone remain a major challenge, even when a large number of potential risk factors are systematically considered (Baune and Thome, 2011; Gaebel et al., 2014).

It is argued that the combination of data from clinical, -omic, structural and functional imaging, electrophysiological and cognitive investigations is likely to be superior to monomodal data for improving predictive accuracy of course of illness and outcome. While multivariate modeling appears in its infancy in schizophrenia, significant progress has already been made in the prediction of transition from the psychosis prodrome to FEP (Koike et al., 2013; Koutsouleris et al., 2012; Shah et al., 2012).

The combination of such data may inform the distinct outcome clusters described by many long-term follow-up studies of schizophrenia (Harding et al., 1987; Hegarty et al., 1994; Huber, 1997; Levine et al., 2011; Rangaswamy, 2012; Thara, 2004). While the nomenclature differs considerably from study to study, they tend to describe four distinct disease trajectories of schizophrenia (Figure 1, upper panel). Patients of Group A experience full functional recovery (FFR) following an initial period of psychotic disturbance, and remain stable in the long term. Patients of Group B have multiple exacerbations of illness and/or poor functioning over time, but achieve FFR in between these episodes. Group C patients demonstrate recurrent exacerbations as well as some enduring functional deficits between episodes. Patient group D is characterized by severe and enduring functional impairment early from disease onset.

It is noteworthy that, for the majority of patients, these disease trajectories emerge only after an initial period of clinical and functional instability (Robinson et al., 2004), lasting 3–4 years on average (Bertelsen et al., 2009; Crumlish et al., 2009; Levine et al., 2011). This time has been referred to as the 'critical period', during which biological, psychological, and social reactions to the illness develop and reach their maximum plasticity (Birchwood et al., 1998). Thus, both the bio-psycho-social profile detectable at first presentation and the modifying dynamic events during the 'critical period' significantly influence long-term clinical

Figure 1. Structured translational approach to describing trajectories of illness course and functional outcome following FEP.



Structured description of disease and functional trajectories in schizophrenia, and translation into clinical practice. Psychiatric systems reveal clinical, cognitive, affective, brain-structural, molecular, and modulating profiles which contribute to phenotypes of illness progression and functional outcome. These, in turn, describe the disease and functional trajectories following the initial critical illness period (groups A–D, upper panel). Translation of this approach into clinical practice involves a multimodal diagnostic process producing data that are combined in a prognostic model, which then describes the most likely illness trajectory and may inform optimal treatments.

outcomes. We do not propose that outcomes are completely pre-determined at disease onset, but that structured assessment and modeling of multivariate cross-sectional and longitudinal predictors can be used to describe the risk of specific outcome trajectories. Evidence from new statistical techniques such as GMM suggests the possibility of clustering individual cross-sectional and longitudinal mental health outcomes into trajectory groups based on specific risk criteria in schizophrenia and other disorders (Levine et al., 2011; Peer and Spaulding, 2007; Wigman et al., 2011; Willke et al., 2012).

Figure 1 shows a systematic approach to the description of disease and functional trajectories of psychotic disorders, and its potential translation into clinical practice. Predictor variables are grouped into key psychiatric systems. These psychiatric systems can be differentiated as follows: a) individual clinical characteristics of a patient, including risk factors such as maternal pregnancy complications, early neurodevelopmental history, and socioeconomic status; b) their neuro-cognitive, affective, and functional profile; c) their brain structure and neural function; d) their molecular profile; and e) modulating prognostic factors such as personality, insight, and resilience (Figure 1). Data from these systems are modeled to derive descriptions of illness trajectories and outcomes. The translation of this model into clinical practice is represented in the lower half of Figure 1. Here, structured assessments feed into computerized prognostic models that are used to determine the best current treatment based on the most likely illness trajectory.

Translation into clinical practice: the need for a complex diagnostic process at disease onset and during the course of the illness

In recent years multivariate prognostic models have proliferated through the medical literature (Steyerberg et al., 2013), and other fields of medicine, such as oncology, have successfully adopted and translated such models to provide individualized risk assessment and treatment (Krishnan et al., 2013). We argue that psychiatry should consider a similar approach across the multiple modes of available data to describe course of illness and functional outcomes following FEP, as depicted in Figure 2. Clinical practice would then require a systematic and structured integration of bio-psycho-social data into an extended diagnostic process (Banati and Hickie, 2009).

Operationalizing an extended diagnostic approach using Bayes' rule

One technique that approximates an extended diagnostic approach in severe mental illness is to use the Odds-Ratio form of Bayes' Rule (McGee, 2002), as described in the Methods section. Using this technique, each new clinical assessment or investigation finding either increases or decreases the probability of a given outcome, thereby approximating the stepwise development of diagnostic or prognostic information in clinical practice across time (Clark, 2009; Clark et al., 2003; Clark et al., 2005; Sox et al., 2013).

Clinical example: probability of long-term functional recovery following FEP

Based on published data from two independent longitudinal studies (Alvarez-Jimenez et al., 2012; Mourao-Miranda et al., 2012), we simulated the effect of combined clinical assessment and structural MRI at first presentation on the probability of developing favorable or unfavorable long-term outcomes.

Figure 2 shows that presence of all five poor prognostic clinical characteristics (male gender, low education level, poor insight, poor premorbid adjustment, non-independent accommodation) plus MRI characteristics indicating chronic course is sufficient to identify with reasonable accuracy the group of patients likely to develop poor long-term outcomes. Conversely, the presence of all five good prognostic clinical characteristics (female gender, post-secondary education, good insight, good premorbid adjustment, and independent living at FEP) plus MRI characteristics indicating a non-chronic/intermittent course confidently identifies those likely to experience favorable long-term outcomes. The extreme upper and lower tree branches in Figure 2 illustrate these trajectories.

When initial assessment shows a mixed probability profile (e.g. presence of all five poor clinical predictors, but normal MRI result), our model indicates that at least one more assessment (here: functional status and negative symptom status 8 months post FEP) is required to obtain clarity over the likely long-term prognosis. Moreover, when clinical characteristics at FEP are indicating an intermediate risk probability (i.e. presence of less than five poor or good clinical predictors), outcome prediction becomes more complex and again requires at least three assessments to obtain improved prognostic accuracy. Of note, for a certain percentage of patients from all groups predictive accuracy remains intermediate despite three assessments, indicating that additional diagnostic modalities may be required.

Discussion

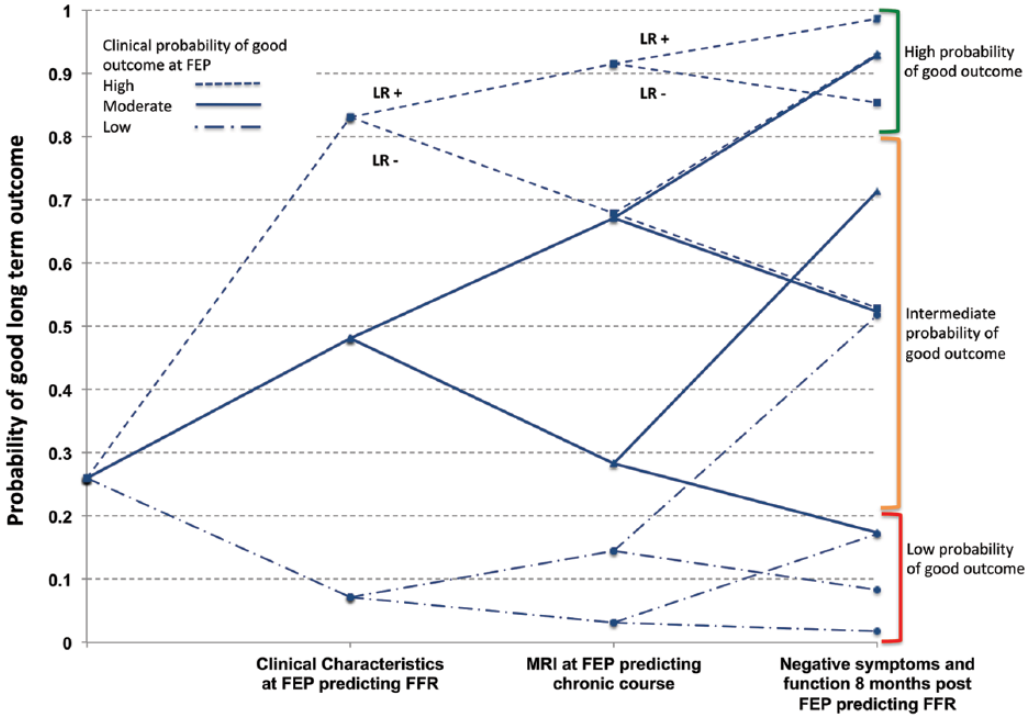
Implications for clinical practice

A staging model of severe mental illness has been developed over recent years, ranging from at-risk states (stages 0 and 1) to unremitting psychosis (stage 4) (Hickie et al., 2013; McGorry et al., 2006). Guided by this model, it is hoped that stage-appropriate treatments, delivered in a timely manner, could arrest the progression to more advanced stages of illness, or may promote regression to an earlier stage.

In this context, the approach to describing illness outcomes discussed in this article may serve two purposes. Firstly, it may stimulate and inform future research into the causes and predictors of illness progression from one stage to the next. Secondly, by adding an early description of the individual's risk of progression to a specific illness stage, it may help the clinician to estimate the value of performing a specific investigation or to make utility-based judgments on treatment selection, thus personalizing the assessment and treatment process and optimizing overall efficiency of care (Hatcher, 1995; Owens et al., 1997; Simon et al., 2006; Sox et al., 2013; Werneke et al., 2012; Yokota and Thompson, 2004). Treatment choices informed by such risk may, for example, involve early clozapine initiation (Kaneda et al., 2010; Remington et al., 2013), targeted early provision of cognitive remediation training or cognitive enhancing treatments (Koike et al., 2013; Medalia and Saperstein, 2013; Wood et al., 2013), early specialized vocational rehabilitation (Killackey et al., 2008), specific neuroprotective strategies (Swerdlow, 2011), or targeted augmentation with anti-inflammatory medications (Sommer et al., 2014) or metabolic modifiers such as metformin (Correll et al., 2013; Guest et al., 2013a Guest et al., 2013b).

Our simulation suggests that this process could be supported by offering a systematic assessment of known clinical risk factors for good or poor outcome following FEP, as well as a structural MRI scan with SVM analysis for each patient presenting with an FEP. On the basis of these two initial investigations, it may be possible to identify groups of patients

Figure 2. Stepwise prediction of functional outcomes following FEP.



From three simulated groups of patients with high, moderate, and low probability of achieving favorable long-term outcome based on their clinical characteristics at FEP, the stepwise evolution of probabilities is shown when MRI at FEP and assessment of negative symptoms and function at 8 months are added as investigations.
LR+: positive likelihood ratio, used to calculate probability progression in case of a positive test result; LR−: negative likelihood ratio, used to calculate probability progression in case of a negative test result.

with very high and very low likelihood for good or poor long-term outcomes with reasonable accuracy. In clinical practice, such a combined assessment process should be achievable, particularly in light of the relatively fast and accessible simplification of SVM technology described by Mourao-Miranda et al. in their study (Mourao-Miranda et al., 2012). However, our model also shows that, for patients presenting with discrepant initial assessment findings, further investigations are required to achieve satisfactory prognostic accuracy. We have modeled an additional clinical assessment of functional status and negative symptoms 8 months following FEP, which could be offered to this intermediate risk group.

While our model focuses on MRI to extend and refine assessment at first presentation, other modalities or forms of investigation may serve a similar purpose, for example the assessment of prognostic serum biomarkers (Schwarz et al., 2012b), electrophysiology (Manchanda et al., 2008), cognitive status (Faerden et al., 2013; Hovington et al., 2013), or serial imaging over time (Lappin et al., 2014). Future work may equally indicate that the best predictive accuracy can be achieved with a more extensive combination of investigative modalities at first presentation. The clinically optimal and most cost-effective sequence of such a combination approach remains to be explored.

Limitations

The clinical example illustrated in Figure 2 seeks to demonstrate the development of probability of FEP outcomes over time with the limitation of combining data from different populations from two single studies with different endpoints. We chose this approach due to the lack of other published investigations of more homogeneous endpoints, reporting sensitivity and specificity data from which the likelihood ratios required for our model can be derived. The scarcity of data of this format in the biomedical literature has been described and criticized previously (Gale et al., 2013). Future work could look to extract and combine more risk data across published studies and databases, or encourage authors to make risk data available in the required formats, and then use meta-analysis to determine more accurate estimates of the relationship between individual risk factors and outcomes (Chuma and Mahadun, 2011).

There are many potential challenges of achieving solid and reliable models of illness trajectory in psychiatry. Firstly, there is a dearth of cross-sectional and longitudinal data sets rich enough to inform the envisaged trajectory modeling strategy, and many previously proposed predictors have not been independently replicated. Secondly, the interaction and interdependence of variables in such a model are extraordinarily complex, requiring mathematical consideration of a multitude of factors. Thirdly, translation into practice has the potential for ethical dilemmas: should a patient be denied certain treatments if evidence suggests that they will do little for their outcome? What about potentially helpful treatment effects that cannot be measured by the model? How would one determine and treat 'outliers', who do well despite a multitude of poor prognostic factors? How is the treatment principle of therapeutic optimism achieved in the context of prognostic modeling? Fourthly, as with all novel clinical approaches, the utility and safety of specific modeling algorithms in practice will require rigorous testing in well-designed randomized placebo-controlled trials, comparing the outcomes of standard treatment decisions with decisions informed by the prognostic model. Tools and algorithms will also require updating over time as new evidence emerges. Lastly, no modeling technique is able to predict the impact of important life events such as losses, physical illness, or new relationships on an individual's course of illness. While the stepwise assessment of the risk for illness progression and outcome may serve as a tool of guidance, it cannot replace the empathic therapeutic relationship.

Conclusion

There is a growing body of evidence concerning the description of disease and outcome trajectories following FEP. To move forward with the translation of this knowledge, we require more richly described multimodal longitudinal data on predictors and outcomes and better integration of these data into multivariate models. By shifting the focus from discrete outcomes, such as relapse, to the description of disease and functional trajectories, it might be possible to accelerate this process with improved prediction validity. Stepwise models of outcome prediction that augment and work alongside the clinical assessment process may be useful in clinical practice, providing best estimates of possible outcome trajectory as information evolves over time. This approach is well represented by probabilistic models based on Bayes' Theorem and decision analysis techniques. Such models could be used to personalize assessment and to support decisions regarding evidence-based treatment, thus supplementing existing staging approaches.

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