



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Baseline psychopathology and relationship to longitudinal functional outcome in attenuated and early first episode psychosis

Cynthia Z. Burton^{a,*}, Ivy F. Tso^a, Ricardo E. Carrión^b, Tara Niendam^c, Steven Adelsheim^d, Andrea M. Auther^b, Barbara A. Cornblatt^b, Cameron S. Carter^c, Ryan Melton^e, Tamara G. Sale^e, Stephan F. Taylor^{a,1}, William R. McFarlane^{f,g,1}

^a University of Michigan, United States of America

^b Zucker Hillside Hospital, United States of America

^c University of California, Davis, United States of America

^d Stanford University, United States of America

^e Oregon Health Sciences School of Public Health, United States of America

^f Maine Medical Center Research Institute, United States of America

^g Tufts University School of Medicine, United States of America

ARTICLE INFO

Article history:

Received 25 October 2018

Received in revised form 28 February 2019

Accepted 28 July 2019

Available online xxxx

Keywords:

Clinical high risk
Attenuated psychosis
Positive symptoms
Negative symptoms
Functioning

ABSTRACT

Background: As efforts intensify to intervene early among those at risk for psychosis, examination of the relationship between presenting psychopathology and long-term functional outcome may guide treatment decision-making and offer a means to prevent or reduce chronic disability.

Methods: Data were collected through the Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP), a multisite national trial testing the efficacy of an early intervention for youth at risk of developing psychosis. Participants were followed prospectively and completed comprehensive evaluations at 6, 12, and 24 months, including the Structured Interview for Prodromal Syndromes (SIPS) and the Global Social and Role Functioning Scales. The present analyses included 327 participants and examined the relationships between baseline symptoms and longitudinal global social and role functioning using a linear mixed modeling approach.

Results: Higher baseline negative symptoms and deteriorated thought process predicted worse social and role functioning in the follow-up period. The effect of negative symptoms on social functioning, however, was moderated by positive symptoms, and the relationship between positive symptoms and social functioning changed over time. Baseline positive symptoms, distress, and level of symptom severity were not predictors of either social or role functioning.

Conclusions: Baseline negative symptoms and thought disorder appear to predict functional outcome for up to two years among adolescents and young adults at risk for psychosis. Developing effective interventions to target these symptoms may be critical to promote functional recovery among those experiencing attenuated symptoms or a first episode of psychosis.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

Given the chronic disability and poor functional outcome often associated with schizophrenia and other psychotic disorders, much attention has shifted in recent years to early detection and intervention among those at risk for psychosis. Originally conceptualized as a 'prodromal' phase of illness, current terminology describes individuals as

"clinical high risk" (CHR), "ultra-high risk" (UHR) or "at risk mental state" (ARMS), all essentially referring to the same condition. Although 10–35% of people with the risk syndrome go on to develop full psychosis within 2 to 2 ½ years, conversion rates continue to increase linearly over lengthier periods (Cannon et al., 2008; Fusar-Poli et al., 2012; Nelson et al., 2013). Worldwide efforts have focused on developing an evidence base for a variety of interventions for adolescents and young adults at risk for or following a first episode of psychosis. Family-aided Community Treatment (FACT) is one such intervention for CHR individuals, while Coordinated Specialty Care (CSC) is intended for individuals experiencing a first episode of psychosis. These programs are team-based, collaborative, and recovery-oriented approaches that typically

* Corresponding author at: University of Michigan Neuropsychology Section, 2101 Commonwealth Blvd, Suite C, Ann Arbor, MI 48105, United States of America.

E-mail address: czburton@umich.edu (C.Z. Burton).

¹ Co-senior authors

involve intensive case management, family psychoeducation, individual or group psychotherapy, supported employment and education, and selective antipsychotic treatment. In the United States, the Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP) found positive effects for a broad range of symptoms and global outcomes for FACT (McFarlane et al., 2015). Similarly, the NIMH Recovery After an Initial Schizophrenia Episode (RAISE) research initiative determined that comprehensive care improved some aspects of functional and clinical outcomes over two years, with more pronounced effects among individuals with a shorter duration of untreated psychosis (Kane et al., 2016). Therefore, with increasing recognition of the benefit of these types of programs, thorough examination of the relationships between baseline presenting psychopathology and longitudinal functional outcome may help refine treatment decision-making and offer a means to prevent or reduce chronic disability.

Among individuals identified as CHR, some evidence suggests that negative and disorganized symptoms are associated with functional outcome. For example, Meyer et al. (2014) found that negative symptoms mediated the relationship between neurocognition and social and role functioning at baseline and 12-month follow-up among CHR individuals in the first phase of the North American Prodrome Longitudinal Study. Similarly, a 2015 study demonstrated that negative symptom severity was uniquely predictive of social functioning, beyond depression/anxiety and neurocognition (Schlosser et al., 2015). In addition, both duration and severity of negative symptoms at baseline have been found to significantly predict social outcome (Carrión et al., 2016). Furthermore, Yung and colleagues recently reported that persistent negative symptoms were associated with poorer psychosocial functioning over a lengthy follow-up period, regardless of transition to psychosis (Yung et al., 2018). Regarding disorganized symptoms, a 2014 study concluded that disorganized symptoms were highly predictive of functional outcome over a 6-year follow-up interval (Ziermans et al., 2014). Disorganized symptoms at baseline also predicted social functioning in another CHR sample (Carrión et al., 2013).

The literature on the effect of positive symptoms on functioning among CHR individuals, however, is inconsistent. Although the presence of attenuated positive symptoms is a main criterion for CHR classification, and logically predicts conversion to psychosis as a clinical outcome, several studies have found that positive symptoms are not strongly or significantly predictive of functional outcome (Carrión et al., 2016; Meyer et al., 2014; Ziermans et al., 2014). Other research suggests, though, that those with more severe positive symptoms at baseline take considerably longer to achieve both symptomatic and functional remission (Lee et al., 2014). It is possible that the effect of positive symptoms on outcome changes over the course of illness or interacts with other symptom dimensions; thus, relationships with outcome cannot be readily revealed by examining its main effect only, as has been the case in previous studies.

While these studies provide useful preliminary information regarding the effect of baseline symptom severity on functional outcome, many were limited by small sample sizes and either narrow measurement of functioning (e.g., examining only social functioning) or use of a global functioning scale that combines symptom-based information with functional status, thereby confounding clinical and functional data. To address some of these limitations, the present study included a larger sample of individuals at varying levels of risk for developing psychosis who were followed longitudinally for up to two years. Specifically, the sample included those with psychosis-like experiences or functional decline, individuals meeting standard criteria of Psychosis-Risk Syndromes, and individuals in the earliest phases of onset of frank psychosis. We tested four empirically derived symptom factors at baseline as predictors of functional outcome, which was separately assessed for social and role functioning (apart from clinical symptom severity). This study also used linear mixed modeling, a type of regression useful for longitudinal data in which observations are not independent. This approach allows for the examination of whether predictors interact

with one another and if their predictive value changes over time. Overall, this large sample, longitudinal study aimed to add to the limited existing evidence base by focusing on symptomatic predictors of functional outcome among CHR individuals, rather than conversion to psychosis. Achieving a better understanding of the long-term functional consequences of presenting symptomatology may allow for more precise allocation of treatment resources at service entry, enhance a personalized medicine approach, and guide the discovery of the relevant neurobiology influencing both symptoms and functioning.

We hypothesized that greater baseline negative symptoms and thought disorganization would significantly predict worse functional outcome. We also conducted exploratory analyses based on the literature in schizophrenia suggesting that the relationship between negative symptoms and functional outcome would interact with positive symptoms and distress. Negative symptoms in schizophrenia are often separated into *primary* negative symptoms, reflecting a core disability linked to poor outcome, and *secondary* negative symptoms, reflecting depression, paranoid withdrawal, extrapyramidal symptoms, etc. (Galderisi et al., 2018; Strauss and Cohen, 2017). The assessment of negative symptoms using standardized instruments in CHR cannot easily distinguish between the two, so we hypothesized that positive symptoms and distress would moderate the effect of negative symptoms on outcome (for example, if negative symptom ratings picked up withdrawal due to paranoia or depression, that would be a secondary negative symptom and not predictive of poor outcome).

2. Methods

2.1. Participants

Participants for these analyses were enrolled in EDIPPP, a multisite national trial testing the efficacy of FACT as early intervention for youth at risk of developing psychosis (McFarlane et al., 2012; McFarlane et al., 2015). Specific inclusion criteria were: (1) age 12–25, (2) living in the site's defined catchment area, and (3) receiving a score of ≥ 1 on any Positive Symptom Scale or ≥ 3 on any Negative Symptom Scale of the Scale of Prodromal Symptoms (SOPS; defined below in Measures). Potential participants were excluded if they (1) were experiencing a current psychotic episode (i.e., a score of 6 on any Positive Symptom Scale for longer than 30 consecutive days), (2) had a prior episode of psychosis or had received antipsychotic medication for 30 days or more at a dosage appropriate to treat a psychotic episode, (3) had an IQ < 70 , (4) did not speak English fluently, (5) were currently a prisoner in the criminal justice system, or (6) had psychotic symptoms due to an acute toxic or medical etiology. It should be noted that EDIPPP employed a risk-based classification, different from traditional CHR criteria. SOPS positive scores were used to classify participants into one of three groups: clinical low-risk (CLR; $n = 86$; sum of positive scores on the SOPS < 7), CHR ($n = 197$; sum of SOPS positive scores ≥ 7 , but not meeting threshold for psychosis), and early first episode psychosis (EFEP; $n = 44$; < 30 days of positive symptoms meeting the threshold for psychosis as determined by the Presence of Psychotic Symptoms or POPS criteria of the SOPS). Participants included in the present analyses ($N = 327$) were 17 years old on average, and the majority were male and Caucasian. Table 1 includes demographic and clinical characteristics of the sample.

2.2. Procedures

EDIPPP study procedures have been fully described elsewhere (McFarlane et al., 2012). Briefly, six participating clinical sites representing ethnically and geographically diverse populations provided community outreach and education, intake assessments, and prospective follow-up visits for two years. Using a risk-based allocation design, CHR and EFEP participants were provided FACT, and CLR

Table 1
Demographic and clinical characteristics of the sample.

Variable	Mean/N	SD/%
Age	16.96	3.3
Male	198	60.6
Race		
Caucasian	201	61.5
African American	31	9.5
Asian American	13	4.0
American Indian/Alaska Native	4	1.2
Native Hawaiian/Pacific Islander	2	0.6
More than one Race	37	11.3
Other Race	24	7.3
GF Social	6.18	1.5
GF Role	5.41	2.4
SOPS Positive score	10.94	5.7
SOPS Negative score	13.37	6.1
SOPS Disorganized score	5.52	3.4
SOPS General score	10.42	4.5

Note. Fifteen participants (5%) were missing racial demographic data. GF and SOPS values reflect baseline scores.

participants were provided monthly phone monitoring. Participants completed comprehensive evaluations at 6, 12, and 24 months.

2.3. Measures

Among others, measures included the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan et al., 2010) and specifically one of its constituent sections called the Scale of Prodromal Symptoms (SOPS). As developed, the SOPS includes sections assessing positive symptoms, negative symptoms, disorganization, and general symptoms (examples below). Previous analysis including 334 EDIPPP participants at baseline identified four empirical factors of the SOPS: positive symptoms (i.e., unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, bizarre thinking), distress (i.e., sleep disturbance, dysphoric mood, impaired tolerance to normal stress), negative symptoms (i.e., social anhedonia, avolition, expression of emotion, experience of emotions and self, odd behavior or appearance, impairment in personal hygiene), and deteriorated thought process (i.e., disorganized communication, ideational richness, occupational functioning, trouble with focus and attention) (Tso et al., 2017). These factor scores were used in the present analyses, which are favorable because they assign the empirical weight to each item, rather than assigning equal weight as with calculating a mean or summed score. Functional outcome was measured with the Global Functioning: Social (GF Social) and Global Functioning: Role (GF Role) Scales (Cornblatt et al., 2007). As outlined by Cornblatt et al. (2007), these scales provide clinician-rated single overall scores between 1 and 10, with 1 indicating extreme dysfunction and 10 representing superior functioning. The scales are rated regardless of etiology of functional impairment or level of clinical symptomatology. Both scales include detailed anchor points designed to be relevant to an adolescent/young adult population; for example, the GF Role scale anchor points refer to performance in school, work, or as a homemaker, depending on age. It also takes into account the individual's overall performance in the role given the level of support required. The GF Social scale assesses the quantity and quality of peer relationships, level of peer conflict, age-appropriate intimate relationships, and involvement with family members (though social contacts outside the family are emphasized).

Of note, two items of the SOPS, social anhedonia (N1) and occupational functioning (N6), clearly overlap with the content of the GF Social and GF Role scales, respectively. To avoid this confound, these two items were removed from the dataset when computing the baseline negative symptoms and deteriorated thought process scores for the current analyses.

2.4. Analyses

The present analyses included 327 participants with baseline SOPS factor scores derived by Tso et al. (2017) and functional ratings for at least one time point. Functioning data were available for 318 participants at baseline, 239 at 6-month follow-up, 236 at 12-month follow-up, and 217 at 24-month follow-up. Linear mixed effect modeling with maximum likelihood estimation was used to examine the relationship between baseline symptoms and social & role functioning over time. For each outcome variable (GF Social and GF Role), successive models were built: first, an unconditional mean model (Model 1) was estimated to compute the intraclass correlation coefficient and confirm the utility of modeling a growth curve. Next, an unconditional linear growth curve model (Model 2) added only visit (time) as a continuous predictor variable. Third, the four baseline symptom predictors were added, as well as two dummy coded clinical group variables to examine any effect related to clinical classification (i.e., CLR vs. CHR vs. EFEP) (Model 3). Non-significant fixed effects were then removed; for initial model-building, alpha for significance was set to $p \leq 0.10$ for each predictor to lean towards broader inclusion, and for the final model a more stringent criterion of $p \leq 0.05$ was used. Then, interaction terms including visit by each of the four symptom predictors were added to examine whether the predictive value of baseline symptoms changed over time. Again, non-significant effects ($p \geq 0.10$) were removed. Two additional interaction terms were then added based on a priori hypotheses regarding the effects of symptom dimensions on one another: positive symptoms by negative symptoms and distress by negative symptoms. Non-significant effects were removed until all remaining predictors were statistically significant at $p < 0.05$. For each model, three indices were used to compare fit: -2 Log Likelihood, Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC). Random effects included intercept and visit (time), and the covariance matrix was unstructured. The final models were those with the lowest -2 Log Likelihood, AIC, and BIC values.

3. Results

Fig. 1 illustrates mean social and role functioning scores at each time point for the three clinical groups.

3.1. Social functioning

The unconditional mean model yielded an intraclass correlation coefficient of 0.46, indicating that 46% of the variance in social functioning ratings were due to interindividual differences and exceeding the suggested minimum cutoff of 25% for the utility of growth curve modeling (Shek and Ma, 2011). Ultimately, nine models were compared (Supplementary Table 1). The best-fitting model included main effects for Negative Symptoms and Deteriorated Thought Process, and Negative \times Visit, Positive \times Visit, and Positive \times Negative interactions (Table 2). Specifically, more severe negative symptoms and deteriorated thought process significantly predicted worse social functioning. The Negative \times Visit interaction indicated that the relationship between negative symptoms and social functioning differed over time, such that more negative symptoms always predicted worse social functioning, though the effect lessened over the follow-up period. Positive symptoms alone were not a significant predictor, but the interaction with visit occurred because the effect of positive symptoms on social functioning differed over time. At baseline, more positive symptoms predicted worse social functioning, although at follow-up time points, more baseline positive symptoms predicted better social functioning. The significant interaction between positive symptoms and negative symptoms indicated that the effect of negative symptom severity on social functioning depended on severity of positive symptoms. More specifically, higher positive symptoms at baseline lessened the deleterious effect of negative symptoms on social functioning.

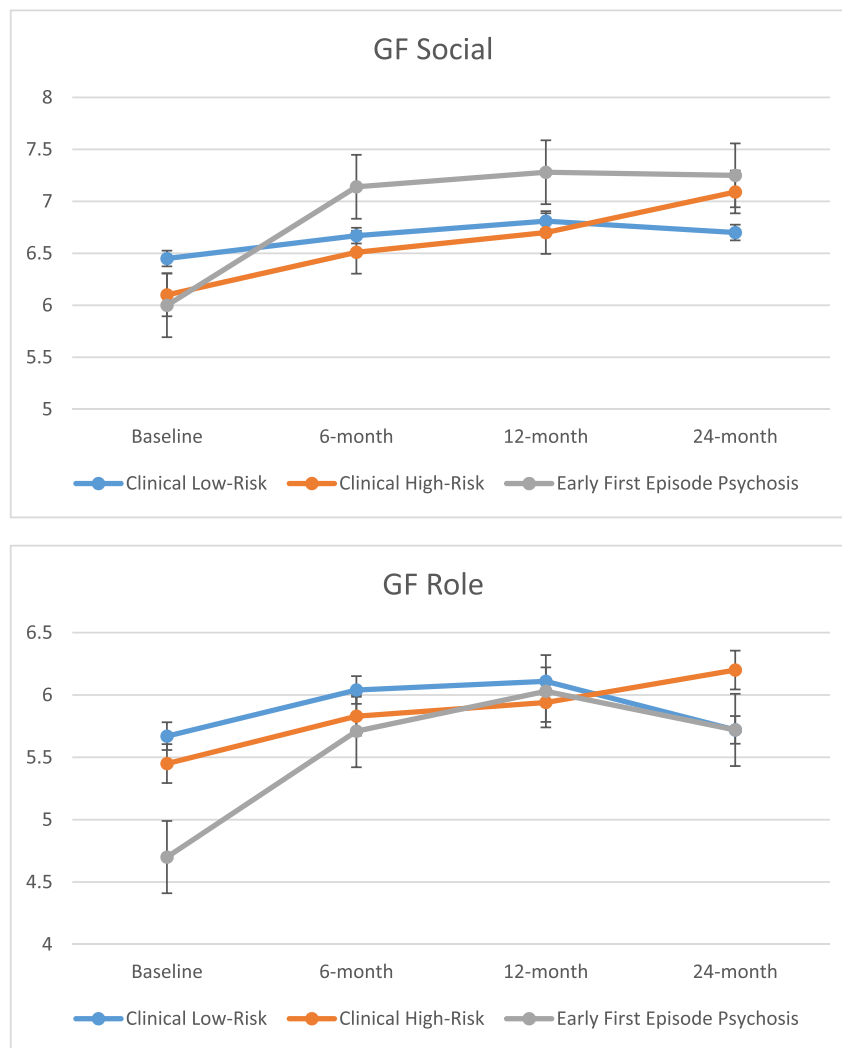


Fig. 1. GF Social and GF Role ratings at each time point.

3.2. Role functioning

The unconditional mean model yielded an intraclass correlation coefficient of 0.49, suggesting that 49% of the variance in role functioning ratings was due to interindividual differences and again exceeding the suggested minimum cutoff for growth curve modeling (Shek and Ma, 2011). Ultimately, six models were compared (Supplementary Table 2). The best-fitting model included significant main effects for visit, negative symptoms, and deteriorated thought process; there were no interactions with time or among symptom types (Table 3). While in general role functioning improved over time, higher baseline negative symptoms and deteriorated thought process predicted worse

role functioning. Model fit worsened with the inclusion of visit by symptom interactions as well as the hypothesized interactions between positive and negative symptoms, and distress and negative symptoms. This suggests that the predictive value of baseline symptoms did not change over time, and did not change based on other-symptom severity.

4. Discussion

This study used linear mixed modeling to examine the relationships between baseline symptom severity and longitudinal functional outcome for up to 24 months among individuals at varying levels of risk for psychosis or in the very early stage of a first psychotic episode; how these effects change over time and interact with one another were also tested. In general, and consistent with our hypothesis,

Table 2
Social functioning final model.

Parameter	Estimate (std error)	df	t	p
Intercept	7.39 (0.16)	348.08	46.88	<0.001
Negative symptoms	−0.66 (0.11)	344.80	−6.15	<0.001
Deteriorated thought process	−0.21 (0.07)	320.12	−3.10	0.002
Visit * positive symptoms	0.01 (0.00)	267.49	2.51	0.013
Visit * negative symptoms	0.01 (0.00)	262.37	3.39	0.001
Positive symptoms * negative symptoms	0.098 (0.03)	362.08	3.31	0.001

Table 3
Role functioning final model.

Parameter	Estimate (std error)	df	t	p
Intercept	6.88 (0.26)	338.40	26.58	<0.001
Visit	0.02 (0.01)	253.46	2.89	0.004
Negative symptoms	−0.36 (0.12)	316.76	−3.00	0.003
Deteriorated thought process	−0.40 (0.11)	318.71	−3.61	<0.001

worse negative symptoms at baseline were robustly associated with worse social and role functioning across time points; the same was true for deteriorated thought process. This finding adds to the existing literature in schizophrenia that negative symptom severity is significantly associated with functioning, and contributes to a 'deficit' or 'persistent' clinical subtype characterized by poor functional outcome and subsequent disability (Ahmed et al., 2015, 2018). Over time, the association between negative symptoms and social functioning decreased slightly, which may represent a treatment effect. Interestingly, the relationship between positive symptoms and social functioning reversed over time, where baseline positive symptoms were related to worse current social functioning but better social functioning at all three follow-up time points. This finding may reconcile some of the mixed literature on the relationship between positive symptom severity and functioning, since cross-sectional analyses or exclusion of interaction terms would not reveal the changing relationship over time. It may also reflect a treatment effect, in that positive symptoms may have responded better to treatment and resulted in better social functioning.

Moreover, these results supported the hypothesis that positive symptoms and negative symptoms interact to affect social functioning, where individuals with more severe positive and negative symptoms at baseline demonstrated better social functioning over time than those with only high negative symptoms. The moderating effect of positive symptoms on the relationship between negative symptoms and social functioning was in line with our prediction, possibly reflecting that the assessment of negative symptoms for those with high positive symptoms included secondary negative symptoms, not necessarily associated with poor outcome in the schizophrenia literature (Ahmed et al., 2018). It is also possible that high symptoms on both dimensions may indicate the development of a disorder other than schizophrenia, but with a better prognosis, such as bipolar disorder or PTSD. In contrast, the hypothesis that distress at baseline would also moderate the relationship between negative symptoms and functioning was not supported. In terms of role functioning at school, work, or home, the relationships between negative symptoms and deteriorated thought process and role functioning were consistent over time (i.e., there were no interactions with time).

Interestingly, neither positive symptoms nor distress at baseline were associated with social or role functioning ratings at follow-up. This appears consistent with the literature in individuals with chronic schizophrenia, in which positive symptoms may be disturbing and attract attention clinically but are not strongly associated with functioning (Rabinowitz et al., 2012). It is also notable that there was no significant effect of clinical group (CLR versus CHR versus EFEP), indicating that these relationships hold regardless of current clinical designation. This also suggests that the finding would hold if treatment were entered as a covariate, since by design the CHR and EFEP groups received active treatment and the CLR group did not.

Overall, these results suggest that negative symptoms and thought disorder are significantly related to functional outcome for up to two years among adolescents and young adults at risk for psychosis. These findings have important implications for researchers and clinicians working with youth at risk for psychosis, particularly as the clinical emphasis shifts from merely preventing 'conversion' to full psychosis to improving functional outcomes regardless of diagnosis, severity, or level of risk. For example, there is growing evidence that psychosocial interventions like Cognitive Behavioral Therapy (CBT) and family psychoeducation are efficacious at reducing symptoms in this population (Devoe et al., 2018; Kane et al., 2016; McFarlane et al., 2015). Although CBT for psychosis often focuses on positive symptoms like delusional ideation or hallucinatory experiences, it could also address defeatist performance beliefs thought to contribute to the development and maintenance of negative symptoms (Campellone et al., 2016; Granholm et al., 2018). Similarly, family psychoeducation emphasizes behavioral activation strategies and family-based behavioral experiments to challenge negative performance expectations on the part of

the individual or the family. Although there is minimal description in the literature regarding interventions for thought disorder specifically, there is some evidence that Cognitive Therapy may reduce the likelihood of transition to psychosis among those at high risk, where transition was partially defined by the severity of conceptual disorganization (Morrison et al., 2004, 2007). It is reasonable to think that consistent participation in structured and goal-directed cognitive psychotherapy could improve disordered thought processes leading to functional deterioration. Moreover, as pharmacological and nutritional agents continue to be developed and tested for this population, focusing on negative symptoms and disorganized thinking as treatment targets in clinical trials may prove to be more beneficial to long-term outcome. In addition, given the widely reported relationship between cognitive deficits and disorganized thinking, one particular avenue for future research would be to include cognitive enhancement therapies that may improve disorganization and ultimately be associated with better functional outcomes.

There are limitations to this study that should be considered. First, although this was a large sample recruited from geographically diverse locations in the United States, there was not sufficient sample size in each racial category to examine them individually or enable comparisons between groups; future studies may benefit from strategic recruitment of racially and ethnically diverse participants. In addition, not all study participants received the same intervention; for example, individuals designated as clinical low-risk did not receive the FACT intervention, and medication was provided based on protocol-driven clinician judgment (and could have contributed to secondary negative symptoms). Thus, heterogeneity of treatment may have contributed to variance in functional outcome and obscured or magnified these results. Another methodological limitation is that the same examiners used their judgment in rating both symptoms and functioning, which could introduce bias or score similarity related to measure invariance; ideally, future studies would include multiple methods of assessing functioning, for example through use of performance-based functional tasks. It should also be noted that CLR participants were recruited on the basis of both positive and negative symptoms, which failed to meet a predefined threshold; this group should not therefore be considered a healthy comparison group. In fact, these findings suggest that those in the CLR group with high negative symptoms would actually be at risk for functional impairment. In addition, many participants were lost to follow-up, and for unknown reasons; it is possible that some had improved and did not wish to continue participation, or that they worsened clinically and were no longer able to participate. Although unavoidable in a longitudinal study, sample selection bias at the follow-up time points could have affected these results. Moreover, the absence of a cross-validation sample limits conclusions about the stability of the final model and the estimates that were generated to compare relative model fits; confirmation of these results in an independent sample would be helpful. We also acknowledge that the assessment of negative symptoms overlaps with social and role functioning impairment. If negative symptoms and poor functioning reflect the same underlying deficit, to state that symptoms "predict" functioning could be problematic and misleading. To minimize this potential misinterpretation, we limited the use of "predict" to the description of the regression models and their results in the [Methods](#) and [Results](#) sections. In our interpretation of the findings, we used words indicating associations without implying causal direction.

In summary, these results provide additional evidence that baseline negative symptoms and deteriorated thought processes are suggestive of adverse social and role functioning up to two years later. Careful assessment of these features among adolescents and young adults at risk for psychosis, as well as provision of effective interventions targeting these symptom dimensions, may be helpful to reduce their long-term functional impact.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.07.048>.

Declaration of Competing Interest

Dr. Taylor receives research support from Vanguard Research/Otsuka Pharmaceutical and Boehringer-Ingelheim. Dr. McFarlane provides training on request to public and not-for-profit agencies in methods for treating patients with early psychosis. All other authors declare that they have no conflicts of interest.

Acknowledgement

This work was supported by the Robert Wood Johnson Foundation (grant number #67525 to WRM), with additional institutional support from the Maine Medical Center Research Institute and the State of Maine. Dr. Burton receives funding from the NAMI Unger Research Fellowship. Dr. Tso receives funding from the National Institutes of Health (5K23MH108823). Dr. Taylor receives funding from the Boledovich Schizophrenia Fund.

Contributors

Authors McFarlane, Niendam, Adelsheim, Auther, Cornblatt, Carter, Melton, and Sale designed the EDIPPP study and wrote the protocol. Authors Burton, Tso, Carrión, Auther, Cornblatt, Taylor, and McFarlane designed and discussed the present study. Author Burton managed the literature searches and analyses. Authors Burton, Tso, and Taylor undertook the statistical analysis, and author Burton wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

The funders of the study have had no role in the study implementation, data collection, analysis, interpretation or reporting of the results in this article. The authors are solely responsible for its contents.

References

- Ahmed, A.O., Strauss, G.P., Buchanan, R.W., Kirkpatrick, B., Carpenter, W.T., 2015. Are negative symptoms dimensional or categorical detection and validation of deficit schizophrenia with taxometric and latent variable mixture models. *Schizophr. Bull.* 41, 879–891. <https://doi.org/10.1093/schbul/sbu163>.
- Ahmed, A.O., Strauss, G.P., Buchanan, R.W., Kirkpatrick, B., Carpenter, W.T., 2018. Schizophrenia heterogeneity revisited: clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. *J. Psychiatr. Res.* 97, 8–15. <https://doi.org/10.1016/j.jpsychires.2017.11.004>.
- Campellone, T.R., Sanchez, A.H., Kring, A.M., 2016. Defeatist performance beliefs, negative symptoms, and functional outcome in schizophrenia: a meta-analytic review. *Schizophr. Bull.* 42, 1343–1352. <https://doi.org/10.1093/schbul/sbw026>.
- Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R., 2008. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch. Gen. Psychiatry* 65, 28–37. <https://doi.org/10.1001/archgenpsychiatry.2007.3>.
- Carrión, R.E., McLaughlin, D., Goldberg, T.E., Auther, A.M., Olsen, R.H., Olvet, D.M., Correll, C.U., Cornblatt, B.A., 2013. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry* 70, 1133–1142. <https://doi.org/10.1001/jamapsychiatry.2013.1909>.
- Carrión, R.E., Demmin, D., Auther, A.M., McLaughlin, D., Olsen, R., Lencz, T., Correll, C.U., Cornblatt, B.A., 2016. Duration of attenuated positive and negative symptoms in individuals at clinical high risk: associations with risk of conversion to psychosis and functional outcome. *J. Psychiatr. Res.* 81, 95–101. <https://doi.org/10.1016/j.jpsychires.2016.06.021>.
- Cornblatt, B.A., Auther, A.M., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D., 2007. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr. Bull.* 33, 688–702. <https://doi.org/10.1093/schbul/sbm029>.
- Devoe, D.J., Farris, M.S., Townes, P., Addington, J., 2018. Attenuated psychotic symptom interventions in youth at risk of psychosis: a systematic review and meta-analysis. *Early Interv. Psychiatry*, 1–15. <https://doi.org/10.1111/eip.12677>.
- Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch. Gen. Psychiatry* 69, 220–229. <https://doi.org/10.1001/archgenpsychiatry.2011.1472>.
- Galderisi, S., Galderisi, S., Mucci, A., Buchanan, R.W., Arango, C., 2018. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry* 5, 664–677. [https://doi.org/10.1016/S2215-0366\(18\)30050-6](https://doi.org/10.1016/S2215-0366(18)30050-6).
- Granholt, E., Holden, J., Worley, M., 2018. Improvement in negative symptoms and functioning in Cognitive-Behavioral Social Skills Training for schizophrenia: mediation by defeatist performance attitudes and asocial beliefs. *Schizophr. Bull.* 44, 653–661. <https://doi.org/10.1093/schbul/sbx099>.
- Kane, J.M., Robinson, D.G., Schooler, N.R., Mueser, K.T., Penn, D.L., Rosenheck, R.A., Addington, J., Brunette, M.F., Correll, C.U., Estroff, S.E., Marcy, P., Robinson, J., Meyer-Kalos, P.S., Gottlieb, J.D., Glynn, S.M., Lynde, D.W., Pipes, R., Kurian, B.T., Miller, A.L., Azrin, S.T., Goldstein, A.B., Severe, J.B., Lin, H., Sint, K.J., John, M., Heinssen, R.K., 2016. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am. J. Psychiatry* 173, 362–372. <https://doi.org/10.1176/appi.ajp.2015.15050632>.
- Lee, T.Y., Kim, S.N., Correll, C.U., Byun, M.S., Kim, E., Jang, J.H., Kang, D.H., Yun, J.Y., Kwon, J.S., 2014. Symptomatic and functional remission of subjects at clinical high risk for psychosis: a 2-year naturalistic observational study. *Schizophr. Res.* 156, 266–271. <https://doi.org/10.1016/j.schres.2014.04.002>.
- McFarlane, W.R., Cook, W.L., Downing, D., Ruff, A., Lynch, S., Adelsheim, S., Calkins, R., Carter, C.S., Cornblatt, B., Milner, K., 2012. Early Detection, Intervention, and Prevention of Psychosis Program: rationale, design, and sample description. *Adolesc. Psychiatry (Hilversum)* 2, 112–124. <https://doi.org/10.2174/2210676611202020112>.
- McFarlane, W.R., Levin, B., Travis, L., Lucas, F.L., Lynch, S., Verdi, M., Williams, D., Adelsheim, S., Calkins, R., Carter, C.S., Cornblatt, B., Taylor, S.F., Auther, A.M., McFarlane, B., Melton, R., Migliorati, M., Niendam, T., Ragland, J.D., Sale, T., Salvador, M., Spring, E., 2015. Clinical and functional outcomes after 2 years in the early detection and intervention for the prevention of psychosis multisite effectiveness trial. *Schizophr. Bull.* 41, 30–43. <https://doi.org/10.1093/schbul/sbu108>.
- McGlashan, T., Walsh, B., Woods, S., 2010. *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-Up*. First. ed. Oxford University Press.
- Meyer, E.C., Carrión, R.E., Cornblatt, B.A., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Heinssen, R., Seidman, L.J., 2014. The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal study. *Schizophr. Bull.* 40, 1452–1461. <https://doi.org/10.1093/schbul/sbt235>.
- Morrison, A.P., French, P., Walford, L., Lewis, S.W., Kilcommons, A., Green, J., Parker, S., Bentall, R.P., 2004. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomized controlled trial. *Br. J. Psychiatry* 185, 291–297.
- Morrison, A.P., French, P., Parker, S., Roberts, M., Stevens, H., Bentall, R.P., Lewis, S.W., 2007. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophr. Bull.* 33, 682–687. <https://doi.org/10.1093/schbul/sbl042>.
- Nelson, B., Yuen, H.P., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D.L., Brewer, W.J., Francey, S.M., Amminger, G.P., Thompson, A., McGorry, P.D., Yung, A.R., 2013. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis the PACE 400 study. *JAMA Psychiatry* <https://doi.org/10.1001/jamapsychiatry.2013.1270>.
- Rabinowitz, J., Levine, S.Z., Garibaldi, G., Bugarski-Kirolo, D., Berardo, C.G., Kapur, S., 2012. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. <https://doi.org/10.1016/j.schres.2012.01.015>.
- Schlosser, D.A., Campellone, T.R., Biagianti, B., Delucchi, K.L., Gard, D.E., Fulford, D., Stuart, B.K., Fisher, M., Loewy, R.L., Vinogradov, S., 2015. Modeling the role of negative symptoms in determining social functioning in individuals at clinical high risk of psychosis. *Schizophr. Res.* 169, 204–208. <https://doi.org/10.1016/j.schres.2015.10.036>.
- Shek, D.T.L., Ma, C.M.S., 2011. Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. *Sci. World J.* 11, 42–76. <https://doi.org/10.1100/tsw.2011.2>.
- Strauss, G.P., Cohen, A.S., 2017. A transdiagnostic review of negative symptom phenomenology and etiology. *Schizophr. Bull.* 43, 712–729. <https://doi.org/10.1093/schbul/sbx066>.
- Tso, I.F., Taylor, S.F., Grove, T.B., Niendam, T., Adelsheim, S., Auther, A., Cornblatt, B., Carter, C.S., Calkins, R., Ragland, J.D., Sale, T., McFarlane, W.R., 2017. Factor analysis of the scale of prodromal symptoms: data from the early detection and intervention for the prevention of psychosis program. *Early Interv. Psychiatry* 11, 14–22. <https://doi.org/10.1111/eip.12209>.
- Yung, A.R., Nelson, B., McGorry, P.D., Wood, S.J., Lin, A., 2018. Persistent Negative Symptoms in Individuals at Ultra High Risk for Psychosis. <https://doi.org/10.1016/j.schres.2018.10.019>.
- Ziermans, T., De Wit, S., Schotthorst, P., Sprong, M., Van Engeland, H., Kahn, R., Durston, S., 2014. Neurocognitive and clinical predictors of long-term outcome in adolescents at ultra-high risk for psychosis: a 6-year follow-up. *PLoS One* 9. <https://doi.org/10.1371/journal.pone.0093994>.