# Multimodal prevention of first psychotic episode through N-acetyl-L-cysteine and Integrated Preventive Psychological Intervention in individuals clinically at high risk for psychosis. Protocol of a randomised, placebo-controlled, parallel-group trial

**Short title: N-acetyl-L-cysteine and psychological prevention**

Stefanie J. Schmidt,[1,2,3] René Hurlemann,[4,5] Johannes Schultz,[4,5] Sven Wasserthal,[4.5] Christian Kloss,[4,5] Wolfgang Maier,[4,6] Andreas Meyer-Lindenberg,[7] Martin Hellmich,[8] Ana Muthesius-Digón,[3] Tanja Pantel,[3] Pia-Sophie Wiesner,[3] Joachim Klosterkötter,[3] Stephan Ruhrmann[3] and the ESPRIT-B1 group

[1] Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland

[2] University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

[3] Department of Psychiatry and Psychotherapy, University of Cologne, Germany

[4] Department of Psychiatry, University Hospital Bonn, Bonn, Germany

[5] Division of Medical Psychology, University Hospital Bonn, Bonn, Germany

[6] German Center for Neurodegenerative Diseases, Bonn, Germany

[7] Central Institute of Mental Health, Mannheim, Germany

[8] Institute of Medical Statistics and Computational Biology, University of Cologne, Germany

Corresponding author:

René Hurlemann

Clinic for Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany

Division of Medical Psychology, University Hospital Bonn, Bonn, Germany

Rene.Hurlemann@ukbonn.de

## Abstract

**Aim:** Meta-analyses indicate positive effects of both antipsychotic and cognitive-behavioural interventions in subjects clinically at high risk (CHR) for psychosis in terms of a delay or prevention of psychotic disorders. However, these effects have been limited regarding social functioning and the relative efficacy of both types of interventions remains unclear. Furthermore, neuroprotective substances seem to be a promising alternative agent in psychosis-prevention as they are associated with few and weak side-effects.

**Methods:** In this multi-centre randomised controlled trial (RCT), we investigate the effects of two interventions on transition to psychosis and social functioning: (1) an Integrated Preventive Psychological Intervention (IPPI) including stress-/symptom-management and social cognitive remediation; (2) N-acetyl-L-cysteine (ACC) as a pharmacological intervention with glutamatergic, neuroprotective and anti-inflammatory capabilities. This is a double-blind, placebo-controlled RCT with regard to ACC and a single-blind RCT with regard to IPPI using a 2×2-factorial design to investigate the individual and combined preventive effects of both interventions. To this aim, a total of 200 CHR-subjects will be randomised stratified by site to one of four conditions: (1) IPPI and ACC; (2) IPPI and Placebo; (3) ACC and Psychological Stress Management; (4) Placebo and Psychological Stress Management. Interventions are delivered over 26 weeks with a follow-up period of 12 months.

**Conclusion**: This paper reports on the rationale and protocol of an indicated prevention trial to detect the most effective and tolerable interventions with regard to transition to psychosis as well as improvements in social functioning and to evaluate the synergistic effects of these interventions.

**Key words:** cognitive remediation, N-Acetyl-L-cysteine, psychosis, prevention, clinical high risk, social cognition

# 1. Introduction

Psychotic disorders are associated with huge individual and societal burden. Therefore, they are among the most expensive brain-related disorders in Europe (Vigo et al., 2016; Wittchen et al., 2011). To fight these detrimental outcomes, indicated prevention approaches have been developed to target individuals at clinical high risk (CHR) for psychosis (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015).

### *1.1 Need for integrated preventive psychological interventions*

Most studies have focused on reducing risk-symptoms by improving symptom-management and found significantly larger effects on transition rates at 6- to 48-month follow-up than control conditions (Schmidt et al., 2015; van der Gaag et al., 2013). However, social functioning is an important but neglected outcome given that substantial functional impairments are already present in CHR-subjects, often worsen until transition to psychosis and are even predictive of it (Addington et al., 2017; Fusar-Poli et al., 2015; Ruhrmann et al., 2010; Velthorst et al., 2017). Current approaches did not produce significantly larger effects on social functioning than control conditions (Schmidt et al., 2015; van der Gaag et al., 2013). One reason for this may be that these approaches were mainly designed to prevent transition to psychosis. Therefore, they were based on cognitive-behavioural therapy (CBT) techniques that are well-established for treatment of positive symptoms of psychosis. Thus, novel interventions are needed to directly target factors modulating social functioning, such as social cognition (Cotter et al., 2017; Glenthøj et al., 2016; Schmidt et al., 2011). Social cognition as the mental operations underlying social interactions comprises the following domains: social and emotional perception, Theory of Mind and social attribution styles (Green et al. 2008; Pinkham et al., 2016). These domains are already impaired in CHR-subjects (Lee et al., 2015; van Donkersgoed et al. 2015). Although the need of social-cognitive remediation for CHR-subjects has also been highlighted in recent reviews (Glenthøj et al., 2017; Statucka & Walder, 2013), there is still a lack of studies evaluating the efficacy of such approaches.

Moreover, current prevention approaches often neglect the fact that, in addition to the markedly increased risk for developing psychosis, CHR-individuals already suffer from multiple mental problems, such as increased levels of distress and poor stress-management skills (Schmidt et al., 2014). Therefore, in line with stress-vulnerability models (Gispen-de Wied et al., 2002; Nuechterlein & Dawson, 1984), psychological interventions to improve stress-management should also be part of psychosis prevention programs.

### *1.2 Need for novel neuroprotective interventions*

Preventive interventions require a most favourable risk-benefit ratio. However, antipsychotics used in most pharmacological trials in this field showed unfavourable side-effects (Ruhrmann et al., 2012). Therefore, potential neuroprotective substances with only few and weak side-effects seem promising. One such neuroprotective agent is N-acetyl-L-cysteine (ACC), which targets dysfunctional glutamatergic neurotransmission, shown to be altered in CHR-subjects (Treen et al. 2016). ACC can elevate brain glutathione (GSH), a major cellular redox regulator and anti-oxidant protecting cells from the damages of reactive oxygen species (Meister & Anderson, 1983). Brain GSH levels have shown to be decreased in the medial prefrontal cortex, in the caudate region and cerebrospinal fluid of drug-naive patients with schizophrenia (Do et al., 2000; Yao et al., 2006). GSH deficiency aggravates neuronal oxidative stress linked to abnormal metabolism of dopamine and glutamate in schizophrenia (Castagné et al., 2004; Smythies, 1997). Polymorphisms of genes involved in GSH synthesis, leading to suppressed protein expression and reduced GSH levels, have also been associated with an enhanced risk for schizophrenia (Gysin et al., 2007; Tosic et al., 2006). ACC increases plasma cysteine levels, thus filling up depleted GSH levels and preventing GSH depletion (Kamboj et al., 2006). In support of this, ACC has been shown to be superior to placebo with regard to symptomatic, cognitive and functional improvements in trials in patients with schizophrenia (Berk et al., 2008; Lavoie et al., 2007; Rapado-Castro et al., 2017; Retsa et al., 2018). The fact that the mechanisms of action of ACC overlap with the GSH-linked pathophysiology of schizophrenia and CHR-states as well as its benign tolerability and safety profile bear the promise to prevent transition to psychosis by augmenting neuronal GSH production.

### *1.3 Relative and combined interventions effects*

ACC is supposed to optimise the effects of psychological interventions (Deepmala et al. 2015). However, with the exception of one randomised controlled trial (RCT) (McGorry et al., 2013), all pharmacological interventions so far were also offered in combination with some kind of psychological intervention, and CHR-subjects in psychological trials were also allowed to take medication (Schmidt et al., 2015). Therefore, positive effects can neither be clearly attributed to one intervention nor do these studies allow any conclusions about the additive effect of both forms of interventions. Thus, multiple head-to-head comparisons are necessary to investigate the relative and combined efficacy of psychological and pharmacological interventions.

Against this background, we aim to investigate the individual and combined preventive effects of two interventions on transition rates and improvements on social functioning in CHR-subjects: 1. of an Integrated Preventive Psychological Intervention (IPPI) focusing on symptom-/stress-management and social-cognitive remediation and 2. ACC as a

pharmacological intervention with glutamatergic, neuroprotective and anti-inflammatory capabilities.

## 2. Methods

### 2.1 Design

This study is a 2×2-factorial trial (see Figure 1): A double-blind, placebo-controlled RCT with regard to ACC and a single-blind RCT with regard to IPPI. This serves to investigate the individual and combined preventive effects with ACC and IPPI as the experimental condition while placebo (Plc) and psychological stress-management (PSM) serve as the control condition (see Figure 1). Consequently, a total of 200 CHR-subjects will be randomised (1:1:1:1) stratified by site to one of four conditions, i.e. 50 participants per condition: (1) IPPI and ACC; (2) IPPI and Plc; (3) ACC and PSM; (4) Plc and PSM. Random assignment is implemented as a 24-7 internet service (ALEA; FormsVisionBV, Abcoude, NL; http://www.formsvision.com/). Allocation sequences are made from permuted blocks of varying length. Randomisation results are given on screen and are sent by e-mail to authorised members of staff. Interventions will be provided for 26 weeks including a follow-up period of 12 months with major assessments at baseline (week -4 to 0), beginning of intervention(s) after randomisation (week 0), at week 12, at the end of intervention(s) (week 26), at 1-year follow-up (week 52) and end of follow-up (week 78) (see Table 1).

*- Please FIGURE 1 and TABLE 1 here -*

### 2.2 Setting

The project with the acronym ESPRIT-B1 (ClinicalTrials.gov Identifier: NCT03149107) is part of the multi-trial "**E**nhancing **S**chizophrenia **P**revention and **R**ecovery through **I**nnovative **T**reatments" consortium (coordinator: Andreas Meyer-Lindenberg, Mannheim). ESPRIT is funded by the German Federal Ministry of Education and Research (BMBF) as part of the German Research Network for Mental Disorders and aims at developing and evaluating innovative interventions to (a) prevent transition to schizophrenia in high-risk individuals, (b) enhance symptomatic and functional recovery in schizophrenia patients in the early phase of the illness, and (c) implement these interventions in clinical practice. ESPRIT-B1 is a multi-centre study involving 11 centres in Germany with established early psychosis centres: RWTH Aachen, RH-FK Alzey, Charité and Vivantes Clinic Berlin, UK Bonn (coordinating centre for ACC), UK Düsseldorf, MHH Hannover, UK Köln (coordinating centre for IPPI), ZI Mannheim, LMU München and UK Tübingen.

Study therapists trained in cognitive-behavioural therapy took part in a 2-day workshop on IPPI and PSM before the begin of the study based on the respective manuals. All parts of this workshop are also available as podcasts and arising problems were additionally discussed in telephone meetings following the workshop. Regular supervision is provided for raters and therapists separately in form of a monthly 1-hour telephone conference and additionally on individual basis via telephone or skype. Each session is audiotaped and rated by two independent individuals based on a well-established fidelity checklist (Haddock, 2002). All participating centres obtained ethical approval by the respective regulatory authority based on the respective trial protocol (January 2017).

### 2.3 Sample

Inclusion, exclusion and withdrawal criteria of this study are shown in Table 2 and are in line with previous studies (Klosterkötter et al., 2005). Participants had to meet any ultra-high risk or basic symptom criterion as assessed by the as assessed by the Structured Interview for Psychosis-Risk Syndromes (SIPS 5.0; McGlashan et al., 2010) and the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007). SIPS and SPI-A have shown good interrater-reliability and construct-validity with good test–retest reliability across short periods of time and assessment modes (McGlashan et al., 2001; Schultze-Lutter et al., 2012; Michel et al., 2014).

*- Please TABLE 2 here -*

### 2.4 Interventions

#### 2.4.1 N-acetyl-L-cysteine (ACC) and placebo (Plc)

Both ACC and Plc are provided as two capsules à 500 mg twice a day, yielding a total dosage of 2000 mg per day. Dosage and mode of intervention were chosen in accordance with a recent trial (Berk et al. 2008) supporting the safety and efficacy of ACC in schizophrenia patients.

#### 2.4.2 Integrated Preventive Psychological Intervention (IPPI)

IPPI was developed in a manualised form with the aim (1) to provide adaptive strategies and/or to reduce maladaptive strategies to cope with stressors efficiently; (2) to enhance understanding of and coping with current and future CHR-symptoms; (3) to provide strategies to improve social-cognitive information-processing and social competencies by optimising encoding-processes of social signals and by reducing social-cognitive biases. Therefore, IPPI comprises four main modules: (1) disorder-related knowledge, (2) stress-management, (3)

symptom-management and (4) social-cognitive remediation (see Table 3). They will be targeted in 22 sessions in an individual setting as single sessions lasting 50 or 90 minutes. The first 21 sessions are scheduled weekly with one booster-session two weeks after the last session. Every module is organised in such a way to increase therapy motivation by activating an individual's resources, personalising contents through selection of the most relevant strategies for each individual and by facilitating experiental learning using multi-sensory materials (e.g. audios, videos of real-life situations, cartoons). Generalisation of effects is enhanced in every module and in particular in the booster-session by elaborating on the relevance of the respective target domain for everyday-life, building upon and optimising already existing strategies, discussing how to deal with potential barriers and by practising new skills in the natural environment between sessions as homework.

*- Please Table 3 here –*

### 2.4.3 Psychological stress-management (PSM)

PSM is based on the well-established relevance of stress and poor coping on the development of psychotic symptoms (Gomes & Grace, 2017) and aims to improve coping with stressful experiences. It is carried out in an individual setting as an active, manualised control condition to ensure that all participants are offered an intervention and potentially benefit from their study participation. PSM comprises 11 sessions à 50 minutes. The first 10 sessions are offered bi-weekly; the last session is scheduled two weeks after session 10. The sessions comprise the following content: Psychoeducation with a narrower model of psychosis development focusing on the role of stress (session 1-3) and stress-management (session 4-10) followed by a closure and booster session (session 11).

### 2.4.4 Prior and concomitant interventions

All previous interventions to manage the trial specific illness are documented in an electronic case report form (CRF). With regard to indications other than the trial specific illness, all previous interventions are allowed and documented in the CRF for the past 3 months before the beginning of the trial. With regard to concomitant interventions, the short-term administration of lorazepam or oxazepam for acute agitation as well as zolpidem, zopiclon or temazepam for sleep disturbances is allowed. Any intake of antipsychotic and/or mood-stabilising medication and/or pregabalin and/or the use of antitussives and nitroglycerin are prohibited during the whole trial-period. All concomitant psychological and/or pharmacological interventions for other indications at the discretion of the investigator are administered in line with current treatment guidelines and documented in the subject`s study record and CRF.

### 2.4.5 Blinding of interventions

Packaging, appearance, colour and taste of the capsules of ACC and Plc are identical to ensure blinding. To maintain blindness of raters, they have access to the (anonymous) patient- and therapy-ID only. Furthermore, IPPI and PSM will be carried out independently from assessors, who are kept unaware of the treatment allocation during all times of the trial. To avoid any form of communication between therapists and assessors, they are not allowed to talk about study subjects with each other and have separate offices as well as study procedures. Study subjects are instructed not to disclose aspects of their intervention to the assessors. Assessors are asked to record any loss of masking of treatment allocation and are asked to guess the allocation. Success of blinding is reported by the ratio of agreements between guessed allocation and real allocation.

## 3. Hypotheses

1. Both ACC and IPPI produce significant effects on transition rates to psychosis and significant improvements in social functioning as primary outcomes compared to control conditions.
2. Both ACC and IPPI produce significant improvements in neuro- and social-cognitive domains as secondary outcomes relative to control conditions.
3. Combined effects of ACC and IPPI on primary and secondary outcomes are significantly larger than those of ACC or IPPI alone.
4. IPPI is hypothesised to produce significantly larger effects on social cognition and social functioning than ACC and PSM.
5. Comparable tolerability is hypothesised for ACC and IPPI.

## 4. Study outcomes

### 4.1 Primary study outcomes

Primary outcome are both transition to psychosis defined as the presence of at least one psychotic symptom for at least one week and social functioning after 18 months (see Table 1).

### 4.2 Secondary study outcomes

As secondary outcomes, we investigate effects on remission of CHR-criteria (i.e. attenuated psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS) and/or cognitive basic symptoms (cognitive disturbances, COGDIS), decrease in overall positive, negative and disorganisation symptoms and depressive symptoms (see Table 1). Furthermore, changes in neuro- and social-cognitive domains are assessed including speed of processing, attention,

verbal learning and memory, executive functions, emotion recognition, social attributions and theory of mind. Additional variables are shown in Table 1. The following treatment-related variables will be assessed: dispense/return of study medication, reasons for study discontinuation, self-reported treatment adherence and reported expectations as well as evaluation regarding treatment. Moreover, safety and tolerability of interventions are evaluated by: (1) Neurologic and general examination (medical history, weight); (2) Identification of adverse events and (3) laboratory assessments including haematology/chemistry panels, a blood/urine pregnancy test at baseline and additionally an urine pregnancy test during the whole intervention period in case of suspected pregnancy and urine drug toxicology screens (in case of positive assessment of transition). Adverse events (AEs) will be summarized by MedDRA code, relatedness, seriousness and severity. Any AE relevant for the evaluation and analysis of the clinical trial has to be documented in the CRF. Every serious adverse event (SAE) that occurs between the first intake of study medication and 30 days after the last administration of study medication must be documented in the CRF and on the SAE report form. The investigator has to report any SAE within 24 hours and every pregnancy detected during the clinical trial to the Clinical Trials Centre Cologne. All cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) during the study has to be reported by the sponsor or Principal/Coordinating Investigator to the responsible supreme federal authority and the respective Ethics Committee and to all clinical trials investigators of the same active substance."

### 4.3 Additional study outcomes

Additional outcomes (see Table 1) are the following: (Functional) magnetic resonance imaging (fMRI) is carried out to investigate functional and structural abnormalities while performing psychological tasks with the aim to detect differences between converters and non-converters. Magnetic resonance spectroscopy (MRS) and blood tests are administered to determine whether receiving ACC effectively elevates glutathione levels. Experience sampling is carried out via smartphones at the beginning and after the intervention to collect participants' responses to questions regarding mood, symptoms, social context, stress, sleep and current location using geo-localising. Furthermore, health economic analyses are conducted to evaluate the cost-effectiveness of these interventions. Biographical, neuropsychological and psychopathology data are clustered using multivariate cluster analysis (RDoC), which yields subgroups of individual variation across these variables within the population under study. Each subject's likelihood of belonging to such a subgroup is used to explore differences in intervention effects as a function of syndrome constellations. Faecal samples are taken for molecular characterisation using 16S rRNA gene sequencing to investigate whether aberrations in microbial community structure and function predict transition to psychosis.

Additionally, biobanking (genetics, epigenetics and proteomic) is used to evaluate whether aberrations predict a CHR-state or transition to psychosis.

## 5. Statistical analyses

### 5.1 Power

Based on recent publications (Schultze-Lutter et al., 2015), we assume a transition risk of about 20% within 18 months. We expect a relative reduction in transition risk of 80% (Schmidt et al., 2015; van der Gaag et al., 2013), i.e. from 20% to 4%. To detect this difference with 80% power at two-sided level 2.5% (i.e. Bonferroni-corrected for two comparisons), an uncorrected chi-square test needs 77 subjects per group (IPPI yes vs. no; ACC yes vs. no). Using the actual time-to-event, the power of corresponding hypothesis tests (i.e. log-rank test, Cox regression) is expected to be slightly higher (Pocock, 1983). To compensate for the influence of about 25% drop-out, 100 CHR-subjects per group (i.e. 200 CHR-subjects in total, 50 per cell) will be included (see Figure 1).

### 5.2 Data management

The data management and monitoring infrastructure will be supplied by the Clinical Trials Centre Cologne including a firewall and daily backup system. Data will be entered online at the trial sites. All changes made to the data are documented in an audit trail. After completion and cleaning of data, the database is locked and the data are stored and exported for statistical analysis by the Clinical Trials Centre.

### 5.3 Data analyses

The full analysis set will be based on the intention-to-treat principle. The primary endpoint “transition within 18 months” will be analysed by time-to-event methods, i.e. Cox regression with main effects ACC, IPPI, age and gender; no interactions. To guard against type I error inflation, the $pp$-values of the Wald statistics will be corrected for two comparisons. Hazard ratios and corresponding 97.5% confidence intervals will be determined. The proportional hazards assumption will be tested by introducing time-dependent covariates. Incomplete observations will be censored. Bias due to possibly informative censoring will be addressed in a sensitivity analysis by inverse probability weighting (IPW) (Cole & Hernan, 2004). The co-primary outcome variables improvement of social functioning after 18 months will be analysed using mixed models for repeated measures (MMRM; fixed effects baseline, ACC, IPPI, time, ACC*time, IPPI*time; ARH1 covariance structure) with corresponding contrasts. Patterns of missing values will be investigated and the impact of various strategies for handling the missing values will be explored in a sensitivity analysis. Subgroup analyses will be done by centre and gender including exploration of possible interactions with interventions. Secondary outcomes

will be analysed either by time-to-event methods, mixed models for repeated measures (MMRM) or using generalised estimating equations (GEEs) to describe and evaluate differences between groups and changes over time. Any clustering effects due to same care providers and centres will be investigated in sensitivity analyses (Boutron et al., 2008).

## 6. Discussion

This paper presents the study rationale and methodology of a large-number multi-centre prevention study in CHR-subjects. The study includes two different types of novel interventions: An Integrated Preventive Psychological Intervention (IPPI) with special emphasis on social cognition to complement and broaden current cognitive-behavioural intervention approaches and a novel pharmacological agent (ACC) with potential neuroprotective effects through its impacts on dysfunctional glutamatergic neurotransmission. The 2×2-factorial design of the study is intended to detect beneficial combinations of these interventions on several outcomes encompassing transition rate, social functioning, risk- and general symptoms, social-cognitive as well as neuropsychological performance and overall tolerability of these interventions. Together with additional data on potential biomarkers and neurobiological mechanisms, our results may support efforts to further personalise interventions for CHR-patients by matching intervention techniques to individual risk constellations and mechanisms of change. Potential limitations of this trial include the large number of assessments and exclusion criteria, which may pose difficulties to the recruitment-process, and the overlap of contents between IPPI and PSM. Taken together, this trial is expected to provide new and well tolerated interventions, thus helping to lower the individual and societal burden of psychotic disorders.

**Acknowledgments**

This study is funded by the German Federal Ministry of Education and Research (BMBF) (project numbers: 01EE1407C, 01EE14071).

ESPRIT-B1 group: Bechdolf, A (Berlin Vivantes); Brockhaus-Dumke, A (RH-RF Alzey); Hirjak, D (ZI Mannheim); Fallgatter, A (UK Tübingen); Frieling, H (MHH Hannover); Janssen, B (UK Düsseldorf); Jessen, F (UK Köln); Kambeitz, J (LMU München); Koutsouleris, N (LMU München); Leopold, K (Vivantes Berlin); Schäfer, C (UK Bonn); Schultze-Lutter, F (UK Düsseldorf); Striepens, N (UK Bonn); Vernaleken, I (RWTH Aachen); Walter, H (Charité Berlin); Wildgruber, D (UK Tübingen).

**Conflict of Interest Statement**

All authors declare that they have no conflict of interest.

**References**


Addington, D., Addington, J., Maticka-Tyndale, E., & Joyce, J. (1992). Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research*, *6*(3), 201-208.

Addington, J., Liu, L., Perkins, D. O., Carrion, R. E., Keefe, R. S., & Woods, S. W. (2017). The role of cognition and social functioning as predictors in the transition to psychosis for youth with attenuated psychotic symptoms. *Schizophrenia Bulletin*, ;*43*(1), 57-63.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington: American Psychiatric Association, 1994.

Bell, M. D., Fiszdon, J. M., Greig, T. C., & Wexler, B. E. (2010). Social attribution test - multiple choice (SAT-MC) in schizophrenia: comparison with community sample and relationship to neurocognitive, social cognitive and symptom measures. *Schizophrenia Research*, *122*(1), 164-171.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., ... Ording-Jespersen, S. (2008). N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biological Psychiatry, 64*(5), 361-368.

Bölte, S., Feineis-Matthews, S., Leber, S., Dierks, T., Hubl, D., & Poustka, F. (2002). The development and evaluation of a computer-based program to test and to teach the recognition of facial affect. *International Journal of Circumpolar Health*, *61*(sup2), 61-68.

Boutron, I., Moher, D., Altman, D. G., Schulz, K. F., Ravaud, P., Group, C. (2008). Extending the CONSORT statement to randomized trials of non-pharmacologic treatment: explanation and elaboration. *Annals of Internal Medicine, 148*(4), 295-309.

Castagné, V., Rougemont, M., Cuenod, M., & Do, K. Q. (2004). Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia. *Neurobiology of Disease, 15(1*), 93-105.

Cole, S. R., & Hernan, M. A. (2004). Adjusted survival curves with inverse probability weights. *Computer Methods and Programs in Biomedicine, 75*(1), 45-49.

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. *Schizophrenia Bulletin*, *33*(3), 688-702.

Cotter, J., Bartholomeusz, C., Papas, A., Allott, K., Nelson, B., Yung, A. R., & Thompson, A. (2017). Examining the association between social cognition and functioning in individuals at ultra-high risk for psychosis. *Australian & New Zealand Journal of Psychiatry*, *51*(1), 83-92.

Deepmala, D., Slattery, J., Kumar, N., Delhey, L., Berk, M., Dean, O., … Frye, R. (2015). Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. *Neuroscience & Biobehavioral Reviews*, *55*, 294-321.

Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory-an introductory report. *Psychological Medicine, 13*, 595-605.

Do, K. Q., Trabesinger, A. H., Kirsten-Krüger, M., Lauer, C. J., Dydak, U., Hell, D., ... Cuenod, M. (2000). Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. *European Journal of Neuroscience, 12*(10), 3721-3728.

Dziobek, I., Fleck, S., Kalbe, E., Rogers, K., Hassenstab, J., Brand, M., ... & Convit, A. (2006). Introducing MASC: a movie for the assessment of social cognition. *Journal of Autism and Developmental Disorders*, *36*(5), 623-636.

Endler, N. S. & Parker, J. D. A. (1990). Multidimensional Assessment of Coping: A critical evaluation. *Personality and Individual Differences, 58*(8), 844-854.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Schultze-Lutter, F., … Yung, A. (2013). The Psychosis High-Risk State a Comprehensive State-of-the-Art Review. *JAMA Psychiatry, 70*, 107-120.

Fusar-Poli, P., Rocchetti, M., Sardella, A., Avila, A., Brandizzi, M., Caverzasi, E., … McGuire, P. (2015). Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *British Journal of Psychiatry, 207,* 198-206.

Gispen-de Wied, C. C., & Jansen, L. M. (2002). The stress-vulnerability hypothesis in psychotic disorders: focus on the stress response systems. *Current Psychiatry Reports*, *4*(3), 166-170.

Glenthøj, L. B., Fagerlund, B., Hjorthøj, C., Jepsen, J. R., Bak, N., Kristensen, T. D., ... Nordentoft, M. (2016). Social cognition in patients at ultra-high risk for psychosis: What is the relation to social skills and functioning? *Schizophrenia Research: Cognition*, *5*, 21-27.

Glenthøj, L. B., Hjorthøj, C., Kristensen, T. D., Davidson, C. A., & Nordentoft, M. (2017). The effect of cognitive remediation in individuals at ultra-high risk for psychosis: a systematic review. *NPJ Schizophrenia*, *3*(1), 20.

Gomes, F. V. & Grace, A. A. (2017). Prefrontal Cortex Dysfunction Increases Susceptibility to Schizophrenia-Like Changes Induced by Adolescent Stress Exposure. *Schizophrenia Bulletin, 43*(3), 592-600.

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. C., ... Heinssen, R. (2008). Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophrenia Bulletin*, *34*(6), 1211-1220.

Gysin, R., Kraftsik, R., Sandell, J., Bovet, P., Chappuis, C., Conus, P., ... Tosic, M. (2007). Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. *Proceedings of the National Academy of Sciences, 104*(42), 16621-16626.

Haddock, G., Devane, S., Bradshaw, T., McGovern, J., Tarrier, N., Kinderman, … Harris, N. (2001). An investigation into the psychometric properties of the Cognitive Therapy Scale for Psychosis (CTSPsy). *Behaviour and Cognitive Psychotherapy, 29*(2), 221-233.

Helmstaedter, C., Lendt, M., & Lux, S. (2001). *VLMT: Verbaler Lern-und Merkfähigkeitstest*. Beltz Test.

Hogan, T. P., Awad, A. G., Eastwood, R. (1983). A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychological Medicine, 45*(3), 223-234.

Kamboj, A., Kiran, R., & Sandhir, R. (2006). Carbofuran-induced neurochemical and neurobehavioral alterations in rats: attenuation by N-acetylcysteine. *Experimental Brain Research, 170*(4), 567.

Kanning, U. P. (2009). *ISK–Inventar Sozialer Kompetenzen.* Göttingen: Hogrefe.

Klosterkötter, J., Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Linszen, D., Birchwood, M., … von Reventlow, H. (2005).The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. *World Psychiatry, 4*(3), 161-167.

Krampen, G. (1991). Fragebogen zu Kompetenz- und Kontrollüberzeugungen (FKK). Hogrefe, Göttingen.

Lavoie, S., Murray, M. M., Deppen, P., Knyazeva, M. G., Berk, M., Boulat, O., …. Do, K. Q. (2007). Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology, 33*, 2187 -99.

Lee, S. Y., Bang, M., Kim, K. R., Lee, M. K., Park, J. Y., Song, Y. Y., ... An, S. K. (2015). Impaired facial emotion recognition in individuals at ultra-high risk for psychosis and with first-episode schizophrenia, and their associations with neurocognitive deficits and self-reported schizotypy. *Schizophrenia Research*, *165*(1), 60-65.

Lehrl, S. (1999). *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B*. Spitta.

Lindström, E., Lewander, T., Malm, U., Malt, U. F., Lublin, H., & Ahlfors, U. G. (2001). Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia. Clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nordic Journal of Psychiatry*, *55*(sup44), 5-69.

Llorca, P. M., Lançon, C., Lancrenon, S., Bayle, F. J., Caci, H., Rouillon, F., & Gorwood, P. (2009). The “Functional Remission of General Schizophrenia”(FROGS) scale:

development and validation of a new questionnaire. *Schizophrenia Research*, *113*(2), 218-225.

McGlashan, T., Miller, T. J., Woods, S. W., Rosen, J. L., Hoffman, R. E., Davidson, L. (2001). Structured Interview for Prodromal Syndromes. New Haven: PRIME Research Clinic, Yale School of Medicine.

McGlashan, T., Walsh, B., & Woods, S. W. (2010). The psychosis-risk syndrome. Handbook for diagnosis and follow-up. New York, N.Y.: Oxford University Press.

McGorry, P. D., Nelson, B., Phillips, L. J., Yuen, H. P., Francey, S. M., Thampi, A., … Yung, A. R. (2013) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. *The Journal of Clinical Psychiatry*, *74*(4), 349-356.

Michel, C., Schimmelmann, B. G., Kupferschmid, S., Siegwart, M., Schultze-Lutter, F. (2014). Reliability of telephone assessments of at-risk criteria of psychosis: a comparison to face-to-face interviews. *Schizophrenia Research, 153*(1), 251-253.

Meister, A., & Anderson, M. E. (1983). Glutathione. *Annual Review of Biochemistry, 52*(1), 711-760.

Montag, C., Dziobek, I., Richter, I. S., Neuhaus, K., Lehmann, A., Sylla, R., … Gallinat, J. (2011). Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. *Psychiatry Research, 186*(2-3), 203-209.

Morosini, P. L., Magliano, L., Brambilla, L., Ugolini, S., & Pioli, R. (2000). Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning. *Acta Psychiatrica Scandinavica*, *101*(4), 323-329.

Muller, H., Hasse-Sander, I., Horn, R., Helmstaedter, C., & Elger, C. E. (1997). Rey Auditory-Verbal Learning Test: structure of a modified German version. *Journal of Clinical Psychology, 53*(7), 663-671.

Nielsen, R. E., Lindström, E., Nielsen, J., & Levander, S. (2012). DAI-10 is as good as DAI-30 in schizophrenia. *European Neuropsychopharmacology*, *22*(10), 747-750.

Nuechterlein, K. H., & Dawson, M. E. (1984). Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophrenia Bulletin*, *10*(2), 160-203.

Petermann, F., & Petermann, U. (Eds.). (2010). *HAWIK-IV: Hamburg-Wechsler-Intelligenztest für Kinder-IV; Manual; Übersetzung und Adaption der WISC-IV von David Wechsler*. Huber.

Pinkham, A. E., Penn, D. L., Green, M. F., & Harvey, P. D. (2015). Social cognition psychometric evaluation: results of the initial psychometric study. *Schizophrenia Bulletin*, *42*(2), 494-504.

Pocock, S. J. (1983). Clinical trials: a practical approach. Chichester West Sussex; New York: Wiley.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and motor skills*, *8*(3), 271-276.

Rapado-Castro, M., Dodd, S., Bush, A. I., Malhi, G. S., Skvarc, D. R., On, Z. X., Berk, M., Dean, O.M. (2017). Cognitive effects of adjunctive N-acetyl cysteine in psychosis. *Psychological Medicine, 47*(5), 866-876.

Resnick, B. A., & Inguito, P. L. (2011). The Resilience Scale: psychometric properties and clinical applicability in older adults. *Archives of Psychiatric Nursing, 25*(1), 11-20.

Retsa, C., Knebel, J. F., Geiser, E., Ferrari, C., Jenni, R., Fournier, M., … Murray, M. M. Treatment in early psychosis with N-acetyl-cysteine for 6months improves low-level auditory processing: Pilot study. *Schizophrenia Research, 191*, 80-86.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., … Klosterkötter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. Arch Gen Psychiatry 67, 241-51.Ruhrmann, S., Klosterkötter, J., Bodatsch, M., Bechdolf, A., Schimmelmann, B. G., Nikolaides, A., ... Schultze-Lutter, F. (2012). Pharmacological prevention and treatment in clinical at-risk states for psychosis. *Current Pharmaceutical Design*, *18*(4), 550-557.

Salize, H. J., Kilian, R. (2010). Gesundheitsökonomie in der Psychiatrie – Konzepte, Methoden, Analysen. Stuttgart: Kohlhammer.

Scher, C. D., Stein, M. B., Asmundson, G. J., McCreary, D. R., Forde, D. R. (2001). The childhood trauma questionnaire in a community sample: psychometric properties and normative data. *Journal of Trauma and Stress, 14*(4), 843-857.

Schlink, S. & Walther, E. (2007). Kurz und gut: Eine deutsche Kurzskala zur Erfassung des Bedürfnisses nach kognitiver Geschlossenheit. *Zeitschrift für Sozialpsychologie, 38*(3), 153-161.

Schmidt, S. J., Mueller, D. R., Roder, V. (2011). Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophrenia Bulletin, 37*(2), 41-54.

Schmidt, S. J., Grunert, V. M., Schimmelmann, B. G., Schultze-Lutter, F., Michel, C. Differences in coping, self-efficacy, and external control beliefs between patients at-risk for psychosis and patients with first-episode psychosis. *Psychiatry Research, 219*, 95-102.

Schmidt, S. J., Schultze-Lutter, F., Schimmelmann, B. G., Maric, N. P., Salokangas, R. K. R., Riecher-Rössler, A., ... Ruhrmann, S. (2015). EPA guidance on the early intervention in clinical high risk states of psychoses. *European Psychiatry*, *30*(3), 388-404.

Schulte, D. (2005). Messung der Therapieerwartung und Therapieevaluation von Patienten (PATHEV). *Zeitschrift für Klinische Psychologie und Psychotherapie, 34,* 176-187.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkötter, J. (2007). Schizophrenia proneness instrument, adult version (SPI-A). *Rome: Giovanni Fioriti*.

Schultze-Lutter, F., Ruhrmann, S., Fusar-Poli, P., Bechdolf, A., Schimmelmann, B., Klosterkötter, J. (2012). Basic symptoms and the prediction of first-episode psychosis. *Current Pharmaceutical Design, 18*(4), 351–357.

Schultze-Lutter, F., Michel, C., Schmidt, S.J., Schimmelmann, B.G., Maric, N.P., Salokangas, R.K., … Klosterkötter, J. (2015). EPA guidance on the early detection of clinical high risk states of psychoses. *European Psychiatry, 30*(3), 405-416.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., ... & Wilkinson, B. (2010). Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *The Journal of clinical psychiatry*, *71*(3), 313-326.

Sibitz, I., Friedrich, M. E., Unger, A., Bachmann, A., Benesch, T., & Amering, M. (2013). Internalized Stigma of Schizophrenia: Validation of the German Version of the Internalized Stigma of Mental Illness-Scale (ISMI). *Psychiatrische Praxis, 40*(2), 83-91.

Smythies, J. R. (1997). Oxidative reactions and schizophrenia: a review-discussion. *Schizophrenia Research, 24*(3), 357-364.

Statucka, M., & Walder, D. J. (2013). Efficacy of social cognition remediation programs targeting facial affect recognition deficits in schizophrenia: a review and consideration of high-risk samples and sex differences. *Psychiatry Research*, *206*(2), 125-139.

Strauss, G. P., Keller, W. R., Buchanan, R. W., Gold, J. M., Fischer, B. A., McMahon, R. P., Kirkpatrick, B. (2012). Next-generation negative symptom assessment for clinical trials: validation of the Brief Negative Symptom Scale. *Schizophrenia Research, 142*(1-3), 88-92.

TheWhoqolGroup. (1998). The World health organization quality of life assessment (WHOQOL): Development and general psychometric properties. *Social Science and Medicine, 46*(12), 1569-1585.

Tosic, M., Ott, J., Barral, S., Bovet, P., Deppen, P., Gheorghita, F., ... Solida, A. (2006). Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene. *The American Journal of Human Genetics, 79*(3), 586-592.

Traue, H. C., Hrabal, V., & Kosarz, P. (2000). AlltagsBelastungsFragebogen (ABF): Zur inneren Konsistenz, Validierung und Stressdiagnostik mit dem deutschsprachigen daily stress inventory. *Verhaltenstherapie und Verhaltensmedizin*, *21*(1), 15-38.

Treen, D., Batlle, S., Mollà, L., Forcadell, E., Chamorro, J., Bulbena, A., & Perez, V. (2016). Are there glutamate abnormalities in subjects at high risk mental state for psychosis? A review of the evidence. *Schizophrenia Research*, *171*(1), 166-175.

Van der Gaag, M., Smit, F., Bechdolf, A., French, P., Linszen, D. H., Yung, A. R., ... Cuijpers, P. (2013). Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophrenia Research*, *149*(1), 56-62.

Van Donkersgoed, R. J. M., Wunderink, L., Nieboer, R., Aleman, A., & Pijnenborg, G. H. M. (2015). Social cognition in individuals at ultra-high risk for psychosis: A meta-analysis. *PloS One*, *10*(10), e0141075.

Velthorst, E., Zinberg, J., Addington, J., Cadenhead, K. S., Cannon, T. D., Carrión, R. E., ... Perkins, D. O. (2017). Potentially important periods of change in the development of social and role functioning in youth at clinical high risk for psychosis. *Development and Psychopathology*, 1-9.

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. *The Lancet Psychiatry*, *3*(2), 171-178.

Weisz, J. R., Chorpita, B. F., Frye, A., Ng, M. Y., Lau, N., Bearman, S. K., ... Hoagwood, K. E. (2011). Youth Top Problems: using idiographic, consumer-guided assessment to identify treatment needs and to track change during psychotherapy. *Journal of consulting and clinical psychology*, *79*(3), 369.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., ...& Fratiglioni, L. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655-679.

Yao, J. K., Leonard, S., & Reddy, R. (2006). Altered glutathione redox state in schizophrenia. *Disease Markers, 22*(1, 2), 83-93.

**Table 1.** Schedule of assessments

| Instrument | Domain | Baseline | Intervention-period | | | | | | | | | | | | Follow-up | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Weeks -4 to 0 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 22 | 26 | 30 | 39 | 52 | 65 | 78 |
| **Psychometric assessments** | | | | | | | | | | | | | | | | | | | |
| SIPS 5.0 | Ultra-high risk criteria; negative, positive, disorganized and general symptoms | | X | | X | | X | | X | | | | | X | | | X | | X |
| SIPS (5.0), P-scale | Transition to psychosis | X | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| SPI-A | Basic symptoms | | X | | X | | X | | X | | | | | X | | | X | | X |
| SOFAS | Social and occupational functioning | X | | | | | | | X | | | | | X | | | X | | X |
| FROGS | Functional recovery in daily and social life | X | | | | | | | X | | | | | X | | | X | | X |
| GFsocial and GFrole | Social and school or work functioning | X | X | | | | | | X | | | | | X | | X | X | X | X |
| BNSS | Negative symptoms | X | | | | | | | | | | | | X | | | X | | X |
| TPA | Identification of 3 main problems | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X |
| M.I.N.I 6.0 | Diagnostic screening, Axis-I diagnosis | X | | | | | | | | | | | | X | | | X | | X |
| Qustions about current substance use | Substance use behaviour | X | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BSI-53 | Symptom level and distress | X | | | | | | | | | | | | | | | | | |
| CISS-24 | Coping strategies | X | | | | | | | | | | | | X | | | X | | X |
| ESPRIT-WHO-QUOL | Health-related quality of life | X | | | | | | | | | | | | X | | | X | | |
| FETZ Chart of Life Events | Current life-events and evaluation | X | | | | | | | X | | | | | X | | | X | | X |
| CTQ | Childhood abuse and neglect | X | | | | | | | | | | | | | | | | | |
| RSA | Resilience | X | | | | | | | | | | | | X | | | X | | X |
| ISMI | Stigma | X | | | | | | | | | | | | X | | | X | | X |
| 16-NFCS | Need for closure | X | | | | | | | | | | | | X | | | X | | X |
| ABF | Daily hassles | | X | | | | | | | | | | | X | | | X | | X |
| FKK | Self-efficacy and locusof control | X | | | | | | | | | | | | X | | | X | | X |
| ISK-K | Social skills | X | | | | | | | | | | | | X | | | X | | X |
| MASC | Social Cognition, Theory of Mind | X | | | | | | | | | | | | X | | | X | | X |
| PoFA | Social cognition, emotion recognition | X | | | | | | | | | | | | X | | | X | | X |
| SAT-MC | Social cognition, social attribution | X | | | | | | | | | | | | X | | | X | | X |
| TMT A & B | Speed of processing, executive functions | X | | | | | | | | | | | | X | | | X | | X |
| AVLT | Verbal learning and memory | X | | | | | | | | | | | | X | | | X | | X |
| DSST | Speed of processing | X | | | | | | | | | | | | X | | | X | | |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DS | Verbal memory | X | | | | | | | | | | | | X | | | X | | |
| MWT-B | Premorbid intelligence | X | | | | | | | | | | | | | | | | | |
| WHO Disability assessment schedule | Disability | X | | | | | | | | | | | | | | | | | |
| **Safety and tolerability assessments** | | | | | | | | | | | | | | | | | | | |
| Neurologic and general examination | | X | | | | | | | | | | | | X | | | | | |
| Weight and hight | | X | | | | | | | | | | | | X | | | | | |
| Pre-intervention symptoms (UKU symptom-list) | | X | X | | | | | | | | | | | | | | | | |
| Adverse Events (UKU symptom-list) | | | X | | | X | | | X | | | X | | X | X | | | | |
| CDSS, complete | | X | | | | | | | X | | | | | X | | | X | | X |
| CDSS, items 1,2,8,9 | | | X | X | X | X | X | X | | X | X | X | X | | X | X | | X | |
| **Laboratory assessments** | | | | | | | | | | | | | | | | | | | |
| Haematology/chemistry panels | | X | | | | X | | | | | | | | X | | | | | |
| Urine/blood pregnancy test | | X | | | | | | | | | | | | | | | | | |
| Urine pregnancy test | | | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | $X^2$ | | | | | | |
| Urine drug toxicology screen | | X | $X^3$ | | $X^3$ | | $X^3$ | | $X^3$ | | $X^3$ | | $X^3$ | $X^3$ | $X^3$ | $X^3$ | $X^3$ | $X^3$ | $X^3$ |
| **Treatment-related assessments** | | | | | | | | | | | | | | | | | | | |
| Psychiatric and medical history | | X | | | | | | | | | | | | | | | | | |
| Prior medication | | | X | | | | | | | | | | | | | | | | |
| Concomitant treatment | | | X | | X | | | X | | | X | | | X | X | X | X | X | X |
| Dispense/return study medication | | | X | | | X | | | X | | | X | | X | | | | | |
| Reasons for study discontinuation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Self-reported treatment adherence | | | | | | X | | | X | | | X | | X | | | | | |
| DAI-10 | | X | | | | | | | X | | | | | X | | | | | |
| PATHEV | | X | | X | | | | | X | | | | | X | | | | | |
| Protocol of psychological interventions (therapist) | | | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment allocation assumption (rater) | | X | | X | | X | | X | | X | | X | X | X | X | X | X | X |
| **Additional assessments** | | | | | | | | | | | | | | | | | | |
| MRI | X | | | | | | | | | | | | X | | | | | |
| MRS – Blood sample (MRS genetics) | X | | | | | | | | | | | | X | | | | | |
| Stool sample for Microbiome | X | | | | | | | | | | | | X | | | X | | |
| Experience sampling (EMA) | X | X | | | | | | | | | | | X | X | | | | |
| Health economic analyses (MRV; WHO-Qol-Bref) | X | | | | | | | | | | | | X | | | X | | |
| Biobanking (blood and saliva samples) | X | | | | | | | | | | | | X | | | | | X |
| RdOc | X | | | | | | | | | | | | | | | | | |

**Abbreviations:** ABF, Daily Stress Inventory (Traue et al., 2005); AVLT, Auditory Verbal Learning Test (et al.,1997; Helmstadter et al., 2001Muller); BNSS, Brief Negative Syndrome Scale (Strauss et al., 2012); BSI-53, Brief Symptom Inventory-53 (Derogatis & Melisaratos, 1983); CDSS, Calgary Depression Scale (Addington et al., 1992); CISS-24, Coping Inventory for Stressful Situations (Endler & Parker, 1990); CTQ, Childhood Trauma Questionnaire (Scher et al., 2001); DAI; Drug Attitude Inventory (Hogan et al., 1983; Nielsen et al., 2002); DS, Digit Span (Petermann & Petermann, 2010); DSST, Digit Symbol Substitution Test (Petermann & Petermann, 2010); ESPRIT-WHO-QUOL, Questionnaire World Health Organization Quality of Life (TheWhoqolGroup, 1998); FKK, Germen Questionnaire on Competence- and Control-beliefs (Krampen, 1991); FROGS, Functional Remission of General Schizophrenia (Llorca et al., 2009); GFS/GFR, Global Functioning Scale: Social and Global Functioning: Role (Cornblatt et al., 2007; Morosini et al., 2000); ISK-K, Inventory of Social Competencies-short version (Kanning, 2009); ISMI, Internalized Stigma of Mental Illness Scale (Sibitz et al., 2013); MASC, Movie for the Assessment of Social Cognition (Dziobek et al., 2007; Montag et al., 2011); M.I.N.I 6.0, Mini International Neuropsychiatric Interview (Sheehan et al., 2010); MRI, magnetic resonance imaging; MRS, Magnetic resonance spectroscopy; MRV, Mannheim Service Use Questionnaire (Salize & Kilian, 2010); MWT-B, Multiple Choice Word Test-B (Lehrl, 1999); NFCS, Need for Closure Scale-16 (Schlink & Walther, 2007); PATHEV, Patient Questionnaire on Therapy Expectations and Evaluation (Schulte, 2005); PoFa, Picture of Facial Affect Test (Bölte et al., 2002); RdOc, Research Domain Criteria; RSA, Resilience Scale for Adults (Resnick & Inguito, 2011); SAT-MC, Social Attribution Test-multiple choice (Bell et al., 2010); SIPS, Structured Interview of Prodromal Syndromes (McGlashan et al., 2010); SPI-A, Schizophrenia Proneness Instrument – Adult Version (Schultze-Lutter et al., 2007); SOFAS, Social Functioning Assessment Scale (APA, 2000); TMT A & B, Trial Making Test A & B (Raitan, 1985); TPA, Top Problem Assessment (Weisz et al., 2012); UKU side-effect rating scale (Lindström et al., 2009).

Note: [1] During intervention +/- 4 days, during follow-up +/- 2 weeks, deviations from starting date don't sum up; [2] In case of suspected pregnancy; [3] Additionally, if transition assessment positive (SIPS 5.0 P-Scale).

**TABLE 2**. Inclusion, exclusion and withdrawal criteria of the study

***Inclusion criteria***

1. Age between 18 and 40 years;
2. Subjects with the ability to follow study-instructions and to attend as well as complete all required visits;
3. Written informed consent of the subject;
4. Clinical High Risk Criteria
   - ESPRIT Ultra-high risk-(UHR) criteria (Attenuated positive symptoms and/or brief limited psychotic symptoms and/or a combination of familial risk or schizotypal disorder with a significant loss of functioning; severity assessed by the Structured Interview for Prodromal Syndromes, SIPS 5.0, McGlashan et al., 2010) and/or
   - The Basic Symptom Criterion 'Cognitive disturbances' (COGDIS) (2/9 cognitive-perceptive basic symptoms; assessed by the Schizophrenia Proneness Instrument – Adult Version, SPI-A, Schultze-Lutter et al., 2004, 2006);

***Exclusion criteria***

Subjects will not be included in the study if any of the following criteria apply:

1. Known history of hypersensitivity to the investigational drug or drugs with a similar chemical structure;
2. Simultaneous participation in another clinical trial investigating medical products within 30 days prior to beginning of this clinical trial. Simultaneous participation in a non-interventional trial is permitted in case the subject is nevertheless willing and able to attend and complete in all required visits of the trial and in case there are no other contradictions;
3. Subjects with a physical or psychiatric condition which at the investigator`s discretion may put the subject at other clinically significant risks than those defined as outcome of this study (i.e. development of a first-episode of psychosis, functional deterioration), may confound the trial results, or may interfere with the subject`s per protocol participation in this clinical trial;
4. Suicidality in terms of subjects scoring higher than 0 on the Calgary Depression Scale for Schizophrenia (CDSS) item 8 on 'suicidality';
5. Subjects with known substance abuse or dependency (DSM-IV-TR);
6. Subjects with hepatic or renal failure;
7. Subjects with known problems of galactose intolerance, clinically significant lactase deficiency or glucose-galactose malabsorption or histamine-intolerance of asthma bronchiale;

8. Subjects with known asthma bronchiale;
9. Subjects with a history of gastrointestinal ulcer;
10. Intake of antitussives (cough-relieving agents);
11. Intake of nitroglycerin;

*Exclusion criteria regarding special restrictions for females:*

12. Current pregnancy or pregnancy planned within 9 months after start of medication or nursing women;
13. Females of child-bearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable or implantable contraceptives or intrauterine devices) unless they are surgically sterilized/hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases;

*Indication specific exclusion criteria:*

14. Having had a psychotic episode for more than 1 week (according to SIPS 5.0);
15. Having symptoms relevant for inclusion potentially arising from a known general medical disorder;
16. Life-time antipsychotic medication for more than 30 days (cumulative number of days) at or above minimum dosage for a 'first-episode of psychosis' range according to current German treatment guidelines (exception: max. dosage for aripiprazole is 5mg/d);
17. Any intake of antipsychotic medication (i.e. independent of duration of intake) within past three months before psychopathological baseline assessments (including self-ratings and screening assessments) at or above minimum dosage of the 'first-episode of psychosis' range according to current German treatment guidelines;
18. Any intake of mood stabilizers (lithium, valproate, carbamazepine, oxcarbazepine, lamotrigine) for more than 30 days (cumulative number of days) during the past three months or any intake during the month before psychopathological baseline assessments (including self-ratings and screening assessments);
19. Any past psychotherapeutic treatment specifically targeting psychotic symptoms or its prevention;

***Withdrawal criteria***

1. Investigator considers that because of safety, behavioural or administrative reasons, the subject needs to be excluded from the trial; Age between 18 and 40 years;

2. New toxicological or pharmacological or severe adverse events occur that invalidate the earlier risk-benefit ratio; Written informed consent of the subject;
3. Study-participant develops a manifest psychotic disorder (SIPS 5.0, McGlashan et al., 2010).

**TABLE 3.** Content and intervention techniques of the Integrated Preventive Psychological Intervention (IPPI)

| Session number | Target domain | Intervention techniques |
|---|---|---|
| **1** | ***Introduction***<br><br>***Problems and Resources*** | - Forming a therapeutic relationship<br>- Exploration of current risk-symptoms and other mental health problems<br>- Functionality of risk-symptoms for social environment and educational/job performance<br>- Introduction of the intervention model and modules of the Integrated Preventive Psychological intervention (IPPI)<br>- Elaboration of main difference between diagnosis and risk<br>- Identification of main resources and problems of each individual |
| **2** | ***Explanation model and psychoeducation*** | - Formulation of an individual explanation model for an at-risk state for psychosis<br>- Linking individual risk-symptoms to the aims of IPPI and integrate them in overall intervention plan<br>- Exploring possible misunderstandings and negative expectations related to the explanation model |
| **3-5** | ***Stress-management*** | - Repetition of explanation model<br>- Linking stressors to risk-symptoms<br>- Introduction of concepts and models of stress and coping<br>- Identifying external/internal triggers of stress, functionality of stress and stress reactions of each individual<br>- Exploring and providing feedback on the individual coping profile<br>- Introduction and practice of the following coping-strategies: mindfulness, progressive muscle relaxation and setting priorities |
| **6-11** | ***Symptom-management*** | - Linking risk-symptoms to the individual explanation model<br>- Normalising and validation of emotions related to risk-symptoms<br>- Psychoeducation about different groups of risk-symptoms (basic symptoms, unusual and delusional thought contents, attenuated hallucinations and self-disturbances) by discussing current explanation models |

| | | |
|---|---|---|
| | | - Formulation of an individual explanation model of risk-symptoms including autobiographical aspects<br>- Optimising and practising cognitive-behavioural strategies to reduce risk-symptoms (e.g. modification of stressors, cognitive biases and dysfunctional schema; generation of alternative explanations and experiments for reality testing) and emotion-focused strategies to deal with emotions triggered by risk-symptoms (e.g. anxiety, anger, depressiveness); cognitive remediation strategies to target deficits in selective attention and inhibition related to basic symptoms and aberrant salience processing |
| **12-15** | ***Social cognition - Affect recognition*** | - Optimising decoding of emotions including facial expressions, gesture and prosody based on exercises with increasing speed and intensity of emotions<br>- Imitation of emotional expressions using a mirror<br>- Computerised exercises to improve automatization of decoding processes |
| **16** | ***Social cognition - Social perception*** | - Identification and training of strategies to identify relevant social signals to interpret interpersonal situations with increasing complexity<br>- Practising strategies based on a series of photos of social interactions to identify and use core social signals (e.g. distance, mutual affection, value of interaction, social roles) |
| **17** | ***Social cognition - Theory of Mind/Empathy*** | - Optimising and practising strategies to enhance theory of mind/empathy based on video-taped social interactions (e.g. to understand ironic messages)<br>- Role-play of difficult social interactions to identify thoughts and feelings of others |
| **18-19** | ***Social cognition – Social attributions*** | - Psychoeducation about common attribution biases (e.g. hostile attribution bias)<br>- Linking attribution biases to deficits in theory of mind/empathy, one`s own self-concept and self-stigma<br>- Identification of cognitive, emotional and social consequences of attribution biases<br>- Exploration of attribution styles based on case-vignettes and own attribution biases in everyday-life<br>- Generation of alternative attributions |
| **20-22** | ***Social*** | - Applying all learned social-cognitive strategies to complex social interactions<br>- Discussing difficulties experienced when applying strategies in natural environment |

| | | |
|---|---|---|
| | ***problem-solving and booster-session*** | - Summarising intervention contents and most important resources and strategies of each individual |

**FIGURE 1.** Study design
Note: ACC, N-Acetyl-Cysteine; IPPI, Integrated Preventive Psychological Intervention; PSM, Psychological Stress-Management; Plc, Placebo.