Cognitive functioning in ultra-high risk for psychosis individuals with and without depression: Secondary analysis of findings from the NEURAPRO randomized clinical trial

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Abstract

Neurocognitive impairments are well established in both ultra-high risk (UHR) for psychosis and major depressive disorder (MDD). Despite this understanding, investigation of neurocognitive deficits in UHR individuals with MDD and its association with MDD within this population, has been scarce. Hence, this study aimed to examine any differences in neurocognition at baseline between those with MDD at baseline and those with no history of MDD, as well as determine whether neurocognitive variables are significantly associated with meeting criteria for MDD at follow-up, while controlling for relevant clinical variables, within a UHR cohort. Data analysis was conducted on 207 participants whose baseline neurocognition was assessed using Brief Assessment of Cognition for Schizophrenia, as part of a trial of omega-3 fatty acids (NEURAPRO) for UHR individuals. While baseline MDD was the strongest predictor, poorer verbal memory and higher verbal fluency were significantly associated with MDD at 12 months ($p=.04$ and $.026$, respectively). Further, higher processing speed was significantly associated with MDD at medium-term follow-up ($p=.047$). These findings outline that neurocognitive skills were independently associated with meeting criteria for MDD at follow-up within UHR individuals, with novel findings of better verbal fluency and processing speed being linked to MDD outcomes. Hence, neurocognitive performance should be considered as a marker of risk for MDD outcomes and a target for management of MDD in UHR.

1. Introduction

High prevalence of depression, with rates ranging between 40-50% is a common characteristic of ultra-high risk (UHR) for psychosis cohorts (Fusar-Poli et al., 2012). Despite this, the primary outcome of interest in most UHR follow-up studies is the transition to psychotic disorder. Thus, prediction of both persistent and incident depression in UHR samples at follow-up has received limited investigation.

Neurocognitive impairments are a well-established feature in UHR cohorts, with performance generally around 0.5 SDs below the average neurocognitive performance of healthy controls in multiple cognitive domains, including verbal learning and processing speed (Hauser et al., 2017). Past studies have differentiated between UHR for psychosis and depression by showing varying neurocognitive impairments across these groups (Schulze et al., 2013). However, to our knowledge, little is known about the relationship between Major Depressive Disorder (MDD) and neurocognitive functioning in those with an at risk mental state for psychosis. According to a recent meta-analysis by Goodall et al. (2018), in studies of young people with MDD, neurocognitive impairments are present in multiple domains including attention, verbal memory, visual memory, IQ and verbal reasoning, with moderate to large effect sizes. Despite broad understanding that neurocognitive abilities are impacted during depression, there remains a lack of agreement regarding the specificity of these impairments (Peters et al., 2017), with no consistent neurocognitive profile having been implicated in MDD (Hammar & Årdal, 2009) and significant shared overlap with the cognitive impairments observed in UHR cohorts.

Lin et al. (2011) in their study of neurocognitive predictors of functional outcomes in UHR, demonstrated that poor functional outcomes at 13-year follow-up were associated with

poor performance in verbal learning and memory, processing speed and attention, and verbal fluency at baseline. They further outlined that examining outcomes other than the transition to psychosis would be valuable in terms of understanding clinical outcomes in UHR. Despite the prevalence of MDD in the UHR population, to our knowledge, no studies have yet investigated the association between neurocognition and MDD in UHR populations.

Zammit et al. (2004) investigated the role of premorbid IQ in predicting a range of psychiatric conditions, in male participants. Results demonstrated that lower IQ was associated with an increased risk of developing depression (adjusted OR=1.19). In keeping with the trait model of neurocognitive impairment, this suggests deficits in neurocognitive ability may be pre-existing vulnerability markers for later development of illness (Allott, Fisher, Amminger, Goodall, & Hetrick, 2016), giving credence to the idea that low IQ can be considered a risk factor for mental health problems other than psychosis.

Studies conducted in populations of adults with MDD have found that out of several clinical and psychological variables, only depressive symptomatology at baseline could significantly improve the prediction accuracy of the presence of MDD at follow-up (Dinga et al., 2018). Previous UHR studies have generally not taken into account meeting criteria for MDD at baseline in addition to neurocognitive status at baseline, to predict follow-up outcomes.

It is often difficult to identify which UHR individuals will develop MDD based solely on presenting clinical features (Fusar-Poli et al., 2012). This demonstrates a clear need for the identification of other factors, such as neurocognitive variables, to further improve prognostic accuracy (Metzler et al., 2016), with evidence suggesting that combining neurocognitive vulnerability markers with presenting clinical features could improve the accuracy of prediction

of psychosis by up to 80% (Koutsouleris et al., 2012). This would also enable identification of risk groups for MDD in UHR through neurocognitive deficits that may be specific for MDD.

Given the lack of research investigating the association between neurocognition and MDD within the at risk mental state, the present study sought to examine neurocognitive functioning in UHR individuals with and without MDD. While controlling for relevant clinical/treatment variables, we also aimed to determine whether neurocognition is an independent predictor of meeting MDD criteria in UHR participants at 12-months and at a mean of 3.4-years follow-up (henceforth referred to as medium-term follow-up). It was hypothesized that: 1) UHR participants meeting criteria for MDD at baseline would have poorer neurocognitive abilities compared to those who do not, and 2) poorer baseline neurocognitive abilities would be significantly associated with meeting criteria for MDD at 12-months and medium-term follow-up, after accounting for clinical characteristics including baseline depression status.

2. Methods

2.1. Study design and participants

A secondary analysis of baseline and follow-up data from an international multi-site randomized controlled trial (RCT; 'NEURAPRO'; trial registration: anzctr.org.au, identifier: 12608000475347) with 304 participants at UHR for psychosis (McGorry et al., 2017), was conducted in the current study. Double-blind randomization was used to assign participants to either the experimental condition in which they were treated with long-chain omega-3 polyunsaturated fatty acids (ω -3 PUFAs), together with cognitive behavioural case management (CBCM), or the control group who received a placebo and CBCM. As found by McGorry et al. (2017), no significant differences existed between the experimental and control conditions with regard to the primary (transition to psychosis) and secondary outcomes of the trial. Treatment

groups were therefore combined for the current study, without further examination of group differences as was done in several other recent analyses of the NEURAPRO data (Bolt et al., 2019; Nelson et al., 2018). Ten early psychosis treatment centres located in Australia (Melbourne, Sydney), Germany (Jena), Switzerland (Basel, Zurich), Austria (Vienna), Denmark (Copenhagen), The Netherlands (Amsterdam), Singapore, and Hong Kong (Pokfulam) took part in the trial and recruited participants. Complete information about the study protocol and inclusion/exclusion criteria are included in Markulev et al. (2017) and McGorry et al. (2017). The present study involved two additional inclusion criteria: 1) participants were required to have completed the baseline neurocognitive battery; and 2) have either met the criteria for MDD at baseline or if not, have no history of MDD. Those with a past history of MDD only were excluded from the current study as—we were unable to determine the number or duration of previous episodes, and this could have influenced the severity of neurocognitive impairment at baseline (Hasselbalch, Knorr, & Kessing, 2011; Weiland-Fiedler et al., 2004). The flow of participants in the present study is shown in Figure 1. Two hundred and seven participants had completed baseline neurocognitive assessments and either met criteria for current MDD or had never met criteria for MDD and therefore, were included in the main analyses.

2.2 Measures

2.2.1 Demographic and clinical characteristics

Participants' age, gender, and highest completed level of education were collected as key demographic characteristics at baseline. The Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002) was used to identify participants who met criteria for MDD at baseline, 12-months, and medium-term follow-up.

The Comprehensive Assessment of the At-Risk Mental State (CAARMS; Yung et al., 2005) was used to assess the UHR criteria and transition to psychosis. Other clinical variables, negative symptom severity was assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), positive psychotic symptom severity using the Brief Psychiatric Rating Scale – Psychotic scale (BPRS-P; Ventura, Nuechterlein, Subotnik, Gutkind, & Gilbert, 2000), and functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS, Goldman et al., 1992).

2.2.2 Neurocognition

The baseline neurocognitive measures which are part of the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004), included: Verbal Memory task measuring verbal memory and learning, Digit Sequencing task measuring working memory, Semantic Fluency and Letter Fluency tasks (scores summed together) measuring verbal fluency, Symbol Coding task measuring speed of processing, Token Motor task and Tower of London task for measurement of motor and executive function, respectively. Z-scores derived from the BACS normative sample were used in analyses for the previous measures. Estimated Full-Scale IQ (FSIQ) was measured using a two-subtest short-form (Vocabulary and Matrix Reasoning subtests) of the Wechsler Adult Intelligence Scale–3rd Edition (WAIS-III; Wechsler, 1997).

2.3 Procedure

Informed written consent was obtained from all participants. Ethics approval for the original RCT was received from the Melbourne Health Human Research Ethics Committee (HREC#: 2008.628). Baseline, 6 months, 12 months, and medium-term follow-up (a mean of 3.4-years follow-up) research assessment were conducted (Nelson et al., 2018).

2.4 Statistical Analyses

The analyses were conducted using IBM® SPSS® Statistics Version 24.0.0. Inspection of missing data and outliers was carried out prior to testing the hypotheses. Examination of any violation of the assumptions of normality, linearity, homoscedascity, or multicollinearity in the dataset was carried out based on guidelines provided by Tabachnick and Fidell (2013). Independent samples t-tests and chi-squared tests were also used to examine group differences in demographics, clinical characteristics and neurocognitive abilities between those with and without MDD at baseline.

Hierarchical logistic regressions were used to examine which neurocognitive domains were associated with MDD at 12-months and medium-term follow-up. In the model, independent variables were entered over two steps: (1) clinical variables (MDD at baseline (Y/N), positive psychotic symptoms (BPRS (Psychotic)), negative symptoms (SANS) and transition to psychosis (Y/N)), and (2) neurocognitive variables.

3. Results

3.1. Participant demographic and clinical information

The sample demographic and clinical information are presented in Table 1. Independent samples t-tests and chi-squared tests were conducted to inspect group differences between individuals with MDD at baseline (N=119) and those without a history of MDD (N=88), due to its likely clinical relevance. Those with MDD at baseline had significantly higher levels of negative ($p<.001$) and positive ($p=.04$) symptoms compared to those without a history of MDD.

3.2 Group differences in baseline neurocognition

The baseline neurocognitive performance of the sample is presented in Table 2. Independent samples t-tests were conducted to examine differences on baseline neurocognition between individuals with MDD at baseline and those without a history of MDD. Those with

MDD at baseline performed significantly worse than those without a history of MDD with regard to verbal memory ($p=.019$), working memory ($p=.009$), and motor speed ($p=.015$). However, using Bonferroni adjusted alpha levels of .007 per test (.05/7), no significant differences in neurocognitive abilities were demonstrated.

3.3 Association between meeting criteria for MDD at 12 months and baseline neurocognition

A hierarchical logistic regression was performed to determine whether, after accounting for clinical factors, neurocognitive performance remained a unique predictor of meeting criteria for MDD at 12-months (see Table 3). After visual inspection of the histograms, assumption of normality was judged to be met. Skewness and kurtosis values ranged from -1.962 to 0.816, and -0.695 to 6.666, respectively. According to guidelines by Tabachnick and Fidell (2013), it was determined that skewness and kurtosis did not make a substantive difference to the analyses, due to the adequate sample size. Further, assumptions of linearity and homoscedascity were demonstrated to be satisfied through examination of scatterplots.

Step 1 of the regression, containing four clinical variables (MDD at Baseline, BPRS-P, SANS and transition to psychosis), was significant, $\chi^2(4, N=100)=38.0, p<.001$. Baseline MDD ($p<.001$) and BPRS-P score ($p=.033$) were shown to make a significant unique contribution to the initial model. The inclusion of neurocognitive variables in Step 2 failed to make a significant improvement to the model, $\chi^2(7, N=100)=13.52, p=.06$. However, the addition of these variables to the model did increase the amount of variance explained at the end of Step 2 ($\chi^2(11, N=100)=51.50, p<.001$). Baseline MDD ($p<.001$), verbal memory ($p=.040$) and verbal fluency ($p=.026$) were the only predictors shown to make a significant unique contribution to the final model. For every unit increase in the verbal memory score, the odds of meeting MDD criteria at 12 months was estimated to decrease by a factor of 48%, after accounting for the other variables.

In contrast, one unit increase in the verbal fluency score was estimated to increase the odds of having MDD at 12 months by 2.49 times. Having MDD at baseline was also shown to greatly increase the odds of meeting MDD criteria at 12 months by 168.51 times.

3.4 Association between meeting criteria for MDD at medium-term follow-up and baseline neurocognition

A hierarchical logistic regression was performed to determine whether, after accounting for covariates, neurocognitive performance remained a unique predictor of meeting criteria for MDD at medium-term follow-up (see Table 4).

Step 1 of the regression, containing four clinical variables (MDD at Baseline, BPRS-P, SANS and transition to psychosis), was shown to be statistically significant, $\chi^2(4, N=97)=29.48$, $p<.001$. Baseline MDD ($p<.001$) was the only significant predictor in the initial model. The inclusion of neurocognitive variables in Step 2 failed to make a significant improvement to the model, $\chi^2(7, N=97)=8.97$, $p=.255$. However, the addition of these variables to the model increased the amount of variance explained at the end of Step 2 ($\chi^2(11, N=97)=38.45$, $p<.001$). Baseline MDD ($p<.001$), and symbol coding ($p=.047$) were the only predictors shown to make a significant unique contribution to the final model. For every unit increase in the symbol coding score, an individual's odds of meeting MDD criteria at medium-term follow-up was increased by 2.09 times. As in the 12-month follow-up, having MDD at baseline was shown to greatly increase the odds of meeting MDD criteria at medium-term follow-up by 22.17 times.

4. Discussion

The present study examined the neurocognitive functioning of UHR individuals with MDD at baseline compared to those without a history of MDD. It also aimed to determine whether domain-specific neurocognition was significantly associated with MDD outcomes at

follow-up, after accounting for MDD status and other relevant clinical variables at baseline. To our knowledge, this is the first study to investigate these questions in the UHR population. After Bonferroni correction no significant differences were found in baseline neurocognitive performance between those with current MDD and no history of MDD. However, the findings demonstrated that poorer verbal memory and higher verbal fluency were significantly associated with MDD at 12 months, whilst higher processing speed was significantly associated with MDD at medium-term follow-up.

4.1 Group differences in baseline neurocognition

Inconsistent with our hypothesis, no significant differences were revealed in baseline neurocognitive measure scores between the groups. Nevertheless, working memory scores were markedly lower at baseline, for those with current MDD compared to those with no history of MDD (small to moderate effect size = 0.38). This finding suggests that comorbid depression may negatively affect working memory within the UHR cohort. There are two plausible explanations for this apparent working memory deficit considering neurobiological and cognitive bases, respectively. First, changes in activation of prefrontal cognitive control regions of those with MDD as determined through neuroimaging, may explain the impairment in working memory (Etkin, Gyurak, & O'Hara, 2013). Second, negative thoughts and ruminations, which are common in MDD, may saturate working memory thus slowing down its related cognitive processes (Gohier et al., 2009). However, it is unclear whether or not this is a state-related impairment as this observation is only cross-sectional and would need to be explored further through a longitudinal analysis to deduce its nature. This deficit underlines the need for treatment approaches for UHR individuals who are depressed, to take into account a person's ability to mentally hold and manipulate relevant information during cognitively-demanding therapy.

It is also important to note that UHR participants with comorbid MDD had significantly higher levels of negative and positive symptoms compared to those without MDD. This result is corroborated by past findings of UHR samples with comorbid depressive disorders which demonstrated more severe positive (Lim et al., 2015) and negative (Fusar-Poli et al., 2012) symptoms than those without the comorbidity. This suggests an interaction between UHR symptomatology and MDD due to the close association between affective and UHR psychopathology. This interaction is therefore also likely to negatively influence neurocognition, including working memory.

4.2 Association between meeting criteria for MDD at 12 months and medium-term follow-up and baseline neurocognition

Partially consistent with our hypothesis, verbal memory and verbal fluency were the only neurocognitive abilities significantly associated with meeting MDD criteria at 12-months. However, the two domains had opposite relationships with the outcome, i.e., lower verbal memory scores, but higher verbal fluency scores were associated with higher log-odds of meeting criteria for MDD at 12-months. The former finding is consistent with previous research showing that verbal memory is one of the more pronounced deficits in UHR. Verbal memory has demonstrated a significant decline over time, and has been particularly sensitive to brain changes and dysfunction (Allott et al., 2019; Hauser et al., 2017; Woodberry et al., 2013). This finding also aligns with meta-analysis findings that identified verbal memory as the most impaired neurocognitive domain in youth with MDD (Goodall et al., 2018). This reaffirms that verbal memory deficits are a common core feature not only for UHR, but also in MDD, underlining the importance of detection and treatment of such deficits for potentially reducing depression risk at follow-up.

Interestingly, similar to higher verbal fluency, faster processing speed at baseline was significantly associated with MDD at medium-term follow-up, inconsistent with our expectation. These findings do not align with the previous findings of Grossman, Best, Harrison, and Bowie (2019), who found no significant differences between individuals with elevated depressive symptoms and healthy controls in the neurocognitive domains of verbal fluency and processing speed. However, this observation is consistent with recent findings by Herniman, Cotton, Killackey, Hester, and Allott (2018), who found that, within individuals with first-episode psychosis (FEP), those who had a comorbid diagnosis of MDD displayed faster processing speed abilities than those who did not. Researchers have speculated that those who are better able to process information may be more attuned to the long-term implications of their diagnosis and the impact that this may have on their lives. This, in turn, may be what leads to their developing and maintaining comorbid MDD (Herniman et al., 2018). While this explanation is purely speculative, it does serve to clarify the current findings, as UHR individuals may similarly be at increased risk of developing MDD if they are more attuned to the impact that being UHR for psychosis may have. Further, previous significant associations between verbal fluency and insight at follow-up (Saeedi, Addington, & Addington, 2007) and higher levels of insight and higher levels of depression (Saeedi et al., 2007; Smith, Hull, Israel, & Willson, 2000) demonstrated in early and chronic psychosis populations would also potentially explain the impact of verbal fluency on MDD at 12 months. Possessing a relatively superior ability to process and express (verbal) information may give rise to more awareness of one's situations and environments thereby, leading to increased emphasis on the negative consequences of their condition. These findings further align with Bora, Yucel, and Pantelis (2009) who showed that affective psychosis is associated with better neurocognition in 6 out of 12 domains including

processing speed, than non-affective psychosis, although the effect sizes of the differences were quite heterogeneous. Given the novelty in this area of research, future efforts should focus on clarifying the link between UHR status, processing speed, verbal fluency, and MDD, to further elucidate potential mechanisms of this relationship.

Despite the unique significance of neurocognition in relation to MDD in UHR, MDD at baseline was by far the strongest predictor of MDD at follow-up (“like” predicting “like”). This is supported by previous evidence in adults with unipolar depression, showing a similar strong relationship with MDD at 2-year follow-up using a machine learning approach (Dinga et al., 2018). This finding highlights the critical importance of effective treatment for depression in UHR at inception to prevent MDD at short- to medium-term follow-up. Further investigation involving the different clinical, psychological and neurocognitive variables in order to gain a better understanding of the prognostic value of the various predictors of MDD outcomes is also warranted.

The findings can be considered clinically important as they provide preliminary evidence for neurocognitive markers that may potentially be an early indication as to whether a UHR individual may or may not develop MDD later on. This suggests the need for considering neurocognitive functioning in monitoring and treatment of depressive symptomatology in the UHR population. Although these findings will require replication before becoming conclusive, the possibilities for such early identification and treatment would have enormous benefit to UHR individuals, with earlier interventions within this group having been linked to more favorable outcomes (Marshall & Rathbone, 2011).

Although the present study findings uniquely add to the current knowledge base, several limitations should be noted. Measurement of neurocognitive performance was only cross-

sectional and hence, constrained the evaluation of the trajectory of neurocognition over the course of the follow-up period and its relationship to MDD outcomes. Thus, a longitudinal analysis of neurocognitive performance and MDD would be an important area for further investigation. Participant attrition was another factor that may have affected the present analysis. There were relatively lower numbers in both groups meeting MDD criteria at follow-up, which may have impacted the examination of the relationship with this outcome due to the insufficient sample size in relation to the number of covariates included in the logistic regression. Sample size also restricted the consideration of other clinical factors or comorbidities such as obsessive-compulsive symptoms (Hur et al., 2012) and substance use (Korver et al., 2010), which may have influenced the neurocognitive performance in the UHR cohort. Further, the interpretation of the higher neurocognitive scores associated with MDD at follow-up was limited, as variables such as insight were not assessed in the current study. Moreover, past history of MDD was not characterized in the current MDD group and was not taken into account in the current study, which hindered the assessment of the influence of past MDD on neurocognition in UHR. Obtaining more precise information on the past MDD diagnoses of the sample and assessing relationships between neurocognition and severity of depressive symptoms would potentially provide further insight into the nature of neurocognitive impairment in those with MDD in UHR. It would also be worthy of future research to investigate how domain-specific neurocognitive functions may relate to medication (e.g., omega-3 fatty acid and antidepressant) effects and real-world functioning in young people with MDD in the UHR for psychosis state. A recent meta-analysis of studies comprising predominantly adults with MDD indicated a modest, positive effect of antidepressants on neurocognitive domains such as immediate memory and processing speed, although no significant effect was shown in working memory (Prado, Watt, & Crowe,

2018). Further investigation of antidepressant and omega-3 treatment effects in younger populations is warranted. A final limitation was that the supposed ‘24-month’ medium-term follow-up assessment in the original study was often, in actuality, completed at a much later date, with assessment dates ranging from 1.5 to 5.7 years after baseline ($M=3.4$ years). Hence, the results may not reflect the predictive abilities of neurocognition at a uniform follow-up period.

In conclusion, the current study findings have shown that significant associations between MDD outcomes and several baseline neurocognitive abilities exist within a UHR-for-psychosis cohort. Deficits in verbal memory, but higher functioning in verbal fluency, were demonstrated to be associated with MDD at 12-months, while higher processing speed was associated with MDD at medium-term follow-up, over and above other clinical variables. The relationship between neurocognition and MDD in UHR should be a focus of investigation in future studies through further incorporation of longitudinal analyses of neurocognitive performance to elucidate its trajectory and relationship with MDD. Similarly, further investigation should be conducted on how neurocognitive abilities relate to the severity of depressive symptoms and other comorbidities, within the UHR population.

References

- Allott, K., Fisher, C. A., Amminger, G. P., Goodall, J., & Hetrick, S. (2016). Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain and Behavior*, 6(10), e00527. doi:10.1002/brb3.527
- Allott, K., Wood, S. J., Yuen, H. P., Yung, A. R., Nelson, B., Brewer, W. J., . . . Lin, A. (2019). Longitudinal Cognitive Performance in Individuals at Ultrahigh Risk for Psychosis: A 10-year Follow-up. *Schizophrenia Bulletin*, 45(5), 1101-1111. doi:10.1093/schbul/sby143
- Andreasen, N. C. (1982). Negative symptoms in schizophrenia: Definition and reliability. *Archives of General Psychiatry*, 39(7), 784-788. doi:10.1001/archpsyc.1982.04290070020005
- Bolt, L. K., Amminger, G. P., Farhall, J., McGorry, P. D., Nelson, B., Markulev, C., . . . Allott, K. A. (2019). Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial. *Schizophrenia Research*, 206, 67-74. doi:10.1016/j.schres.2018.12.013
- Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *The British Journal of Psychiatry*, 195(6), 475-482.
- Dinga, R., Marquand, A. F., Veltman, D. J., Beekman, A. T., Schoevers, R. A., van Hemert, A. M., . . . Schmaal, L. (2018). Predicting the naturalistic course of depression from a wide range of clinical, psychological, and biological data: a machine learning approach. *Translational psychiatry*, 8(1), 241.
- Etkin, A., Gyurak, A., & O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in clinical neuroscience*, 15(4), 419-429.
- First, M., Spitzer, R. L., Gibbon, M., & Williams, J. (2002). *Structured Clinical Interview for DSM-IVTR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute.
- Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., . . . McGuire, P. (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry*, 69(3), 220-229.
- Gohier, B., Ferracci, L., Surguladze, S. A., Lawrence, E., El Hage, W., Kefi, M. Z., . . . Le Gall, D. (2009). Cognitive inhibition and working memory in unipolar depression. *Journal of Affective Disorders*, 116(1-2), 100-105.
- Goodall, J., Fisher, C., Hetrick, S., Phillips, L., Parrish, E. M., & Allott, K. (2018). Neurocognitive functioning in depressed young people: A systematic review and meta-analysis. *Neuropsychology review*, 28, 216-231.
- Grossman, M., Best, M. W., Harrison, A. G., & Bowie, C. R. (2019). Comparison of the neurocognitive profiles of individuals with elevated psychotic or depressive symptoms. *Early Intervention in Psychiatry*, 13(4), 928-934. doi:10.1111/eip.12713
- Hammar, Å., & Årdal, G. (2009). Cognitive functioning in major depression-a summary. *Frontiers in human neuroscience*, 3, 26.
- Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *Journal of Affective Disorders*, 134(1-3), 20-31.

- Hauser, M., Zhang, J. P., Sheridan, E. M., Burdick, K. E., Mogil, R., Kane, J. M., . . . Correll, C. U. (2017). Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and to Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis. *Journal of Clinical Psychiatry*, 78(1), E28-E40. doi:10.4088/JCP.15r10197
- Herniman, S. E., Cotton, S. M., Killackey, E., Hester, R., & Allott, K. A. (2018). Co-morbid depressive disorder is associated with better neurocognitive performance in first episode schizophrenia spectrum. *Journal of Affective Disorders*, 229, 498-505.
- Hur, J.-W., Shin, N. Y., Jang, J. H., Shim, G., Park, H. Y., Hwang, J. Y., . . . Kwon, J. S. (2012). Clinical and neurocognitive profiles of subjects at high risk for psychosis with and without obsessive-compulsive symptoms. *Australian & New Zealand Journal of Psychiatry*, 46(2), 161-169.
- Korver, N., Nieman, D. H., Becker, H. E., Van de Fliert, J. R., Dingemans, P. H., de Haan, L., . . . Linszen, D. H. (2010). Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. *Australian and New Zealand Journal of Psychiatry*, 44(3), 230-236.
- Koutsouleris, N., Gaser, C., Patschurek-Kliche, K., Scheuerecker, J., Bottlender, R., Decker, P., . . . Meisenzahl, E. M. (2012). Multivariate patterns of brain-cognition associations relating to vulnerability and clinical outcome in the at-risk mental states for psychosis. *Human brain mapping*, 33(9), 2104-2124.
- Lim, J., Rekhi, G., Rapisarda, A., Lam, M., Kraus, M., Keefe, R. S., & Lee, J. (2015). Impact of psychiatric comorbidity in individuals at Ultra High Risk of psychosis—Findings from the Longitudinal Youth at Risk Study (LYRIKS). *Schizophrenia research*, 164(1-3), 8-14.
- Lin, A., Wood, S., Nelson, B., Brewer, W., Spiliotacopoulos, D., Bruxner, A., . . . Yung, A. (2011). Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophrenia research*, 132(1), 1-7.
- Markulev, C., McGorry, P. D., Nelson, B., Yuen, H. P., Schaefer, M., Yung, A. R., . . . Schlögelhofer, M. (2017). NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. *Early Intervention in Psychiatry*, 11(5), 418-428.
- Marshall, M., & Rathbone, J. (2011). Early intervention for psychosis. *Cochrane Database of Systematic Reviews*(6).
- McGorry, P. D., Nelson, B., Markulev, C., Yuen, H. P., Schäfer, M. R., Mossaheb, N., . . . Berger, G. E. (2017). Effect of ω -3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. *JAMA psychiatry*, 74(1), 19-27.
- Metzler, S., Dvorsky, D., Wyss, C., Nordt, C., Walitza, S., Heekeren, K., . . . Theodoridou, A. (2016). Neurocognition in help-seeking individuals at risk for psychosis: Prediction of outcome after 24 months. *Psychiatry research*, 246, 188-194.
- Nelson, B., Amminger, G. P., Yuen, H. P., Markulev, C., Lavoie, S., Schafer, M. R., . . . McGorry, P. D. (2018). NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders-medium-term follow-up and clinical course. *NPJ Schizophrenia*, 4(1), 11. doi:10.1038/s41537-018-0052-x

- Peters, A. T., Jacobs, R. H., Crane, N. A., Ryan, K. A., Weisenbach, S. L., Ajilore, O., . . . West, A. E. (2017). Domain-specific impairment in cognitive control among remitted youth with a history of major depression. *Early Intervention in Psychiatry*, 11(5), 383-392.
- Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychology review*, 28(1), 32-72.
- Saeedi, H., Addington, J., & Addington, D. (2007). The association of insight with psychotic symptoms, depression, and cognition in early psychosis: a 3-year follow-up. *Schizophrenia research*, 89(1-3), 123-128.
- Schulze, C., Zimmermann, R., Gschwandtner, U., Pflueger, M. O., Rapp, C., Studerus, E., & Riecher-Rössler, A. (2013). Can cognitive deficits facilitate differential diagnosis between at-risk mental state for psychosis and depressive disorders? *Early Intervention in Psychiatry*, 7(4), 381-390.
- Smith, T. E., Hull, J. W., Israel, L. M., & Willson, D. F. (2000). Insight, symptoms, and neurocognition in schizophrenia and schizoaffective disorder. *Schizophrenia bulletin*, 26(1), 193-200.
- Tabachnick, B. G., & Fidell, L. S. (2013). *Using multivariate statistics* (6 ed.). Boston: Pearson.
- Weiland-Fiedler, P., Erickson, K., Waldeck, T., Luckenbaugh, D. A., Pike, D., Bonne, O., . . . Neumeister, A. (2004). Evidence for continuing neuropsychological impairments in depression. *Journal of Affective Disorders*, 82(2), 253-258.
- Woodberry, K. A., McFarlane, W. R., Giuliano, A. J., Verdi, M. B., Cook, W. L., Faraone, S. V., & Seidman, L. J. (2013). Change in neuropsychological functioning over one year in youth at clinical high risk for psychosis. *Schizophrenia research*, 146(1-3), 87-94.
- Yung, A. R., Yung, A. R., Pan Yuen, H., McGorry, P. D., Phillips, L. J., Kelly, D., . . . Killackey, E. (2005). Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian and New Zealand Journal of Psychiatry*, 39(11-12), 964-971.
- Zammit, S., Allebeck, P., David, A. S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry*, 61(4), 354-360.

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Conflict of Interest

All authors declare no conflict of interest.

Contributors

S.M. co-designed the study, undertook the literature search, conducted the statistical analyses and wrote the first draft of the manuscript. K.A. co-designed the study, assisted with statistical analysis, and the writing of the first draft of the manuscript. H.P.Y. assisted with the statistical analyses and writing of the first draft of the manuscript. P.G.A, J.F., L.B and B.N. contributed to the study design and assisted with the writing of the first draft of the manuscript. All remaining authors contributed to the study design and the final draft of the manuscript.

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Figure(s)

Table 1

Demographic and Clinical Information of UHR Participants who met criteria for MDD at Baseline

Characteristic	Statistics	MDD at Baseline (N = 119)	No history of MDD (N = 88)	<i>p</i> value
Age	<i>M (SD)</i>	19.74 (4.75)	18.59 (4.35)	.08
<i>Gender</i>				.72
Males	% (N)	58.90 (53)	41.11 (37)	
<i>Completed level of Education</i>				.24
No tertiary studies	% (N)	80.67 (96)	86.36 (76)	
Trade or Technical Training	% (N)	12.61 (15)	11.36 (10)	
Undergraduate University Course	% (N)	6.72 (8)	2.27 (2)	
<i>Clinical Characteristics</i>				
<u>Depression severity (MADRS)*</u>	<u><i>M (SD)</i></u>	<u>24.01 (8.91)</u>	<u>15.98 (6.32)</u>	<u>.00</u>
Positive symptoms (BPRS-P)*	<i>M (SD)</i>	8.77 (2.66)	8.01 (2.51)	.04
Negative symptoms (SANS Total)**	<i>M (SD)</i>	22.81 (13.42)	15.97 (12.79)	.00
Social and Occupational Functioning (SOFAS)	<i>M (SD)</i>	50.56 (11.78)	51.80 (11.01)	.45
<u>Frequency of Substance use (ASSIST)</u>	<u><i>M (SD)</i></u>	<u>10.03 (7.87)</u>	<u>9.42 (8.43)</u>	<u>.59</u>
<u>Treatment group (Received omega-3)</u>	<u>% (N)</u>	<u>50.42 (60)</u>	<u>53.41 (47)</u>	<u>.67</u>
<u>Total number of CBCM sessions</u>	<u><i>M (SD)</i></u>	<u>10.11 (6.54)</u>	<u>11.40 (5.93)</u>	<u>.17</u>
<u><i>Status at Follow-up</i></u>				
Transitioned to Psychosis	% (N)	14.29 (17)	15.91 (14)	.75
<i>or had no history of MDD</i>				

Note. * $p < .05$; ** $p < .001$; N = Number of Participants; M = Mean; SD = Standard Deviation; BPRS-P = Brief Psychiatric Rating Scale-Psychotic Subscale; SANS = Scale for the Assessment of Negative Symptoms; SOFAS = Social and Occupational Functioning Assessment Scale; MADRS = Montgomery-Asberg Depression Rating Scale; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test; CBCM = Cognitive Behavioural Case Management.

Table 2

Z-Scores on Neurocognitive Variables of the UHR Participants who met criteria for MDD at Baseline

Neurocognitive Characteristic	MDD at Baseline ($N = 119$)	No history of MDD ($N = 88$)	t value	p value	Effect size
WAIS-III FSIQ Estimate	101.48 (13.46)	103.77 (16.07)	1.08	.28	0.16
BACS Verbal Memory and Learning	-0.46 (1.84)	0.12 (1.52)	2.37	.02	0.34
BACS Working Memory	-0.54 (1.09)	-0.12 (1.18)	2.63	.01	0.38
BACS Motor Function	-0.55 (1.16)	-0.16 (1.02)	2.47	.02	0.35
BACS Verbal Fluency	-0.41 (1.07)	-0.37 (1.14)	0.25	.80	0.04
BACS Processing Speed	-0.38 (1.30)	-0.10 (1.11)	1.62	.11	0.23
BACS Executive Function	0.15 (1.24)	0.20 (1.29)	0.26	.79	0.04

or had no history of MDD

Note. WAIS-III = Wechsler Adult Intelligence Scale – 3rd Edition; BACS = Brief Assessment of Cognition in Schizophrenia; N = Number of Participants.

Table 3

Hierarchical Logistic Regression of Clinical characteristics and Neurocognitive variables as Predictors of MDD at 12-months

Variables	<i>B</i>	<i>SE (B)</i>	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% C.I. Odds Ratio	
							Lower	Upper
Step 1								
Baseline MDD	3.98**	1.07	13.69	1	.000	53.26	6.49	437.37
SANS total	0.02	0.02	0.58	1	.445	1.02	0.98	1.05
BPRS-P	-0.25*	0.12	4.54	1	.033	0.78	0.62	0.98
Transitioned to Psychosis	.08	0.97	0.01	1	.933	1.09	0.16	7.33
Step 2								
<u>Baseline</u> MDD at baseline	5.13**	1.35	14.35	1	.000	168.51	11.87	2391.63
SANS total	0.03	0.03	1.20	1	.274	1.03	0.98	1.08
BPRS-P	-0.27	0.15	3.33	1	.068	0.76	0.57	1.02
Transitioned to Psychosis	-0.38	1.34	0.08	1	.775	0.68	0.05	9.37
WAIS-III IQ	0.02	0.03	0.40	1	.526	1.02	0.97	1.07
Verbal Memory	-0.73*	0.35	4.24	1	.040	0.48	0.24	0.97
Digit Sequencing	0.71	0.43	2.66	1	.103	2.03	0.87	4.75
Token Motor Task	0.20	0.35	0.34	1	.561	1.22	0.62	2.41
Verbal Fluency	0.91*	0.41	4.96	1	.026	2.49	1.12	5.58
Symbol Coding	0.17	0.38	0.21	1	.651	1.19	0.57	2.50

Tower of London	-0.17	0.36	0.22	1	.639	0.84	0.42	1.72
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Note. * = $p < .05$; ** = $p < .001$; MDD = Major Depressive Disorder; *B* = Unstandardized regression coefficient; *SE* = Standard Error; Wald = Wald Statistic; *df* = Degrees of Freedom; BPRS-P = Brief Psychiatric Rating Scale-Psychotic Subscale; SANS = Scale for the Assessment of Negative Symptoms WAIS-III = Wechsler Adult Intelligence Scale (3rd ed.).

Table 4

Hierarchical Logistic Regression of Clinical characteristics and Neurocognitive variables as Predictors of MDD at ~~24-months~~medium-term follow-up

Variables	<i>B</i>	<i>SE (B)</i>	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% C.I. Odds Ratio	
							Lower	Upper
Step 1								
Baseline MDD	2.90**	0.69	17.67	1	.000	18.19	4.70	70.36
SANS total	-0.00	0.02	0.00	1	.947	1.00	0.96	1.04
BPRS-P	-0.09	0.11	0.72	1	.396	0.91	0.73	1.13
Transitioned to Psychosis	0.96	0.76	1.63	1	.202	2.62	0.60	11.50
Step 2								
Baseline MDD	3.10**	0.77	16.29	1	.000	22.17	4.92	99.79
SANS total	0.01	0.03	.09	1	.767	1.01	0.96	1.06
BPRS-P	-0.07	0.14	.25	1	.619	0.94	0.72	1.22
Transitioned to Psychosis	0.96	0.83	1.33	1	.249	2.60	0.51	13.18
WAIS-III IQ	0.02	0.03	.58	1	.445	1.02	0.97	1.08
Verbal Memory	-0.09	0.23	.14	1	.708	0.92	0.58	1.45
Digit Sequencing	-0.28	0.34	.64	1	.424	0.76	0.39	1.49
Token Motor Task	-0.16	0.31	.28	1	.597	0.85	0.47	1.55
Verbal Fluency	-0.67	0.41	2.71	1	.100	0.51	0.23	1.14

Symbol Coding	0.74*	0.37	3.95	1	.047	2.09	1.01	4.31
Tower of London	0.29	0.33	.75	1	.387	1.33	0.69	2.57

Note. * = $p < .05$; ** = $p < .001$; MDD = Major Depressive Disorder; B = Unstandardized regression coefficient; SE = Standard Error; Wald = Wald Statistic; df = Degrees of Freedom; BPRS-P = Brief Psychiatric Rating Scale-Psychotic Subscale; SANS = Scale for the Assessment of Negative Symptoms WAIS-III = Wechsler Adult Intelligence Scale (3rd ed.).

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